A Review of the Scientific Literature As It Pertains to Gulf War Illnesses

VOLUME 8

PESTICIDES

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RAND

The research described in this report was sponsored by the Office of the Secretary of Defense (OSD). The research was conducted in RAND's National Defense Research Institute, a federally funded research and development center supported by the OSD, the Joint Staff, the unified commands, and the defense agencies under Contract No. DASW01-95-C-0059.

ISBN: 0-8330-2682-8

Published 2000 by RAND
1700 Main Street, P.O. Box 2138, Santa Monica, CA 90407-2138
1200 South Hayes Street, Arlington, VA 22202-5050
RAND URL: http://www.rand.org/
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MR_1018/8-OSD

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PREFACE

Veterans of the Persian Gulf War report a variety of physical and psychological symptoms, some of which remain unexplained. In an effort to determine the extent to which these symptoms may be related to Gulf War service and to develop policies to better deal with health risks in future deployments, the Secretary of Defense designated a special assistant to oversee all Department of Defense (DoD) efforts related to the illnesses of Gulf War veterans. The Office of the Special Assistant for Gulf War Illnesses (OSAGWI) is charged to do everything possible to understand and explain the illnesses, to inform veterans and the public of its progress and findings, and to recommend changes in DoD policies and procedures to minimize such problems in the future.

This literature review, one of eight commissioned by the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses, summarizes the existing scientific literature on the health effects of the classes of pesticides that may have affected military personnel who served in Operations Desert Shield and Desert Storm (ODS/DS). The eight RAND reviews are intended to complement efforts by the DoD and other federal agencies to understand the full range of health implications of service in that conflict.

The other seven RAND literature reviews deal with chemical and biological warfare agents, depleted uranium, oil well fires, pyridostigmine bromide, immunizations, infectious diseases, and stress. These represent plausible causes of some of the illnesses Gulf War veterans have reported.

The reviews are intended principally to summarize the scientific literature on the known health effects of given exposures to these risk factors. Where available evidence permits, the other seven reviews also summarize what is known about the range of actual exposures in the Gulf War and assess the plausibility of each risk factor as a cause of illness. A RAND report complementary to this review examines the exposure of Gulf War veterans to pesticides through an ex-

tensive survey;[1] consequently, this review does not detail the actual range of pesticide exposures during ODS/DS. Statements related to the Gulf War experience should be regarded as suggestive rather than definitive, for more research on health effects and exposures remains to be completed before definitive statements can be made. Recommendations for additional research are included where appropriate.

The RAND reviews are limited to literature published or accepted for publication in peer-reviewed journals, books, government publications, and conference proceedings. Unpublished information is occasionally used, but only to develop hypotheses. The present review uses literature published before completion of the initial draft, but some additional references have been included, primarily in response to peer review.

This work is sponsored by the Office of the Special Assistant and was carried out jointly by RAND Health's Center for Military Health Policy Research and the Forces and Resources Policy Center of the National Defense Research Institute. The latter is a federally funded research and development center sponsored by the Office of the Secretary of Defense, the Joint Staff, the unified commands, and the defense agencies.

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[1]Fricker, R. D., et al., *Pesticide Use During the Gulf War: A Survey of Gulf War Veterans,* Santa Monica, CA: RAND, MR-1018/12-OSD, 2000.

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BACKGROUND

Iraq invaded Kuwait in August 1990. The United States and several other nations responded to this invasion by sending troops to the Persian Gulf. After a period of preparation, these troops fought both an air and a ground war. Hostilities ended in March 1991 after less than three months of combat. The Department of Defense (DoD) has estimated that nearly 700,000 U.S. troops served in Operations Desert Shield and Desert Storm (ODS/DS).

Many veterans of that conflict have reported a range of health problems. The most commonly reported symptoms include joint pains, sleep disorder, memory loss, and fatigue. Some of these symptoms are self-reported more frequently by Gulf War veterans than by persons who did not deploy to the Gulf. These reported health problems are of continuing concern to veterans and policymakers alike. This concern has prompted efforts to evaluate whether exposures of veterans to various risk factors during ODS/DS might be linked to their reported symptoms.

PURPOSE OF THE STUDY

This report is part of the ongoing effort to gain a better understanding of the possible causes of undiagnosed symptoms reported by some ODS/DS veterans. It examines the scientific literature on the potential health effects of pesticides that were present during ODS/DS. A majority of the American troops who served in the conflict probably were exposed to pesticides, including repellents. Although toxicity may vary by individual, improper use of certain classes of pesticides can result in symptoms similar to those reported by some Persian Gulf War veterans (PGWV).

This report reviews literature on 12 of the 35 pesticides that are likely to have been used during ODS/DS. It focuses on these 12 because the Office of the

Special Assistant for Gulf War Illnesses (OSAGWI) considers them to be of potential concern because of either toxicity or expected exposure:

- One organochlorine pesticide (lindane)
- One repellent (DEET)
- Two pyrethroid pesticides (permethrin, *d*-phenothrin)
- Five organophosphate pesticides (azamethiphos, chlorpyrifos, diazinon, dichlorvos, malathion)
- Three carbamate pesticides (bendiocarb, methomyl, propoxur)

This review summarizes reports in the scientific literature of known pesticide exposures or doses and related health outcomes. It should be read in conjunction with two other studies: *Pesticide Use During the Gulf War: A Survey of Gulf War Veterans* (Fricker et al., 2000), a review of the findings from a survey of some 2,000 PGWV regarding patterns of pesticide use during the Gulf War; and *Pesticides Environmental Exposure Report* (OSAGWI, 2000), a report being prepared by OSAGWI that investigates pesticide exposures during ODS/DS and draws conclusions based on all the available evidence.

PESTICIDES EXAMINED

Lindane

Lindane belongs to the organochlorine pesticide class. Few organochlorines are in use today, and lindane has not been produced in the United States since 1977, although it is imported in multiple forms for pharmacological and industrial use. Lindane has been used on a wide variety of insect pests in agricultural, public health, and medicinal applications. However, the U.S. Environmental Protection Agency (EPA) restricts its use, and it can be applied only by certified pesticide applicators.

Two lindane products were shipped to the Gulf, where they were used in dust form during ODS/DS as delousing agents. The primary route of potential exposure in veterans was dermal; lindane can be absorbed efficiently through the skin. The dust formulation used in the Gulf would also make inhalation a feasible route.

Lindane has been used for many years, is well known, and has been extensively studied. Its effects are primarily neurotoxic. Lindane generally produces a rapid response and was designed to increase insect respiration to lethal levels. Acute human exposure can result in neurologic changes, including hyperexcitability, tremor, seizure, and coma. The symptoms are generally reversible

with supportive care, although ingestion of large amounts of lindane has resulted in death. Epidemiologic studies in the literature also suggest the possibility of subtle long-term neurologic and reproductive health effects; however, subjects in these studies were exposed to a number of different potentially toxic substances, making it difficult to attribute findings specifically to lindane.

Acute human exposure has usually resulted from accidents either in the manufacture of lindane or in its application in agricultural settings. Acute symptoms reported in humans exposed to lindane include headache, nausea, vomiting, restlessness, ataxia (loss of muscular coordination), tremor, and excitability. Seizure has been reported with more extensive exposures, although specific levels at the times of exposure are not reported.

Few studies specifically evaluate the effects of chronic dermal exposure to lindane, since the intended use of lindane for treating parasitic infection (e.g., lice) generally requires only a single application. However, some studies document human hematological manifestations, including bone marrow hypoplasia and aplastic anemia, following prolonged dermal exposures.

Individuals employed in the manufacture of lindane are exposed to a combination of hexachlorocyclohexane (HCH) isomers (chemical forms) with different effects in biological systems. (Lindane is the gamma isomer.) Humans are also exposed to lindane as an environmental toxicant. Lindane has been used in vaporizers and included among other chemicals in wood preservatives and has been used as an agricultural pesticide. Some situations have precipitated unintentional prolonged exposures to low levels of lindane in the environment. Reports in the literature are either anecdotal or of an epidemiologic case-control nature, where subjects may have been exposed to a number of chemical toxicants simultaneously, making it difficult to attribute specific effects to individual chemical exposures.

Because of the potential risks associated with lindane, its use is no longer recommended as the first-line drug therapy for treating scabies and body lice. Although it should be used with caution, when used appropriately, lindane is generally considered a safe and effective pesticide.

DEET

N,N-Diethyl-*m*-toluamide, also known as DEET, is an aromatic amide that repels a wide range of insects. DEET was first developed by the U.S. Department of Agriculture for military use in 1946, and it has been estimated that approximately 38 percent of the U.S. population uses DEET-containing repellents annually. DEET insect repellent is part of a complete repellent system used by U.S. military personnel. Three different DEET products were shipped to the

Gulf, where they were applied to the skin in cream, liquid, or stick forms. Until 1989, the standard-issue insect repellent of the U.S. military consisted of 75 percent DEET in an alcohol base. This has been replaced with a slow-release, polymer-based product containing 33 percent DEET, which is also available to the general public.

DEET can enter the body through several pathways, including dermal and ocular exposures, inhalation, and ingestion. It is an ideal permeant of skin and has been reported to accelerate the dermal penetration of pharmaceuticals, raising the concern that DEET may also increase dermal penetration of pesticides, since they are often used together. Uncertainty about how much DEET humans absorb complicates any assessment of effects. Generally, the magnitude of DEET that permeates the skin is closely related to the repellent formulation.

Animal studies have shown DEET to affect the cardiovascular and nervous systems. As with many pesticides, the majority of health effects reported to be caused by DEET result from acute exposure. In fact, no evidence in the literature suggests that chronic low-level exposure to DEET will result in long-term effects (with the exception of rare reports of scarring). Therefore, there is no evidence to suggest such a scenario is of great concern in predicting the potential health effects of DEET on PGWV.

Most reviews of DEET toxicity conclude that the risk of adverse effects from the use of DEET-containing repellents as directed by the label appears low. This conclusion is based on reviews of human effects reports, animal toxicology, and possible alternate etiologies for symptoms reported in most patients. In fact, hypersensitivity may be required for severe acute toxic effects to occur, and a suite of data from animal studies generated to support DEET registration provides no evidence of adverse long-term effects related to DEET exposure. Generally, patients who are reported to present severe symptoms related to DEET use recover without reported further effects.

A correlation between the concentration of DEET in a repellent and the frequency or severity of effects is not supported by the literature. Further, it is difficult to quantify consistently the temporal relationship between the onset of central nervous system (CNS) symptoms and exposure to DEET, but the reaction is generally rapid, as is the resolution in most cases. There have been relatively few severe adult effects related to DEET exposure. While a pattern of potentially severe neurotoxicity in children who have been exposed to DEET is emerging, the total number of reported cases is very small compared with the population exposed. This pattern has not been observed in adults. The reasons for this disparity are unknown but may relate to a different surface-area-to-volume ratio in children than in adults.

Concern about the interactive effect of DEET with other chemicals may be warranted, but the available literature is not adequate to permit definitive conclusions at this point. As difficult as it is to extrapolate the results of animal studies to long-term human effects, the presence of chemical interactions compounds the uncertainty inherent in this process. This is not to say, however, that further research should not be undertaken. A prudent approach may be first to determine more accurately which exposures warrant further study. Research to explain the broad variety of outcomes associated with DEET exposure may also be warranted, especially to explain cases of hypersensitivity.

Pyrethroids

Pyrethroids are synthetic pesticides based on the pyrethrins, which are derived from chrysanthemums. Pyrethrins are a "natural" environmental product that is of low toxicity to mammals. They degrade quickly in sunlight, and the cost of reapplying them has limited their widespread agricultural use. Pyrethroids have been synthesized to be similar to pyrethrins but more stable in the environment. Some commercial pyrethroid products also contain organophosphate (OP) or carbamate insecticides because the rapid paralytic effect of pyrethrins on insects is not always lethal. Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates.

Two pyrethroid pesticides are of interest in the Gulf War setting: permethrin and *d*-phenothrin. As part of the DoD Insect Repellent System, permethrin was issued in ODS/DS as a ready-to-use insect repellent labeled for use on clothes such as the battle dress uniform (BDU) and bed netting. The second compound, *d*-phenothrin, is an indoor-use aerosol insecticide, used most commonly for spraying bed netting (to kill insects trapped inside after installation) or spraying inside aircraft to prevent transport of insects.

The literature discussing permethrin stresses its relative safety. Individuals with occupational exposure have been reported to experience facial skin sensations (burning or itching), usually within a few hours of exposure. Ingestion of permethrin has resulted in epigastric pain, nausea, and vomiting. Acute poisoning symptoms relate primarily to the effects of pyrethroids on the nervous system and include dizziness, headache, nausea, anorexia, and fatigue. Very large exposures cause muscle fasciculation and altered consciousness.

After permethrin was introduced as an alternative treatment for head lice in humans, data were gathered regarding possible adverse effects. Approximately 2.2 adverse events were reported per 1,000 administrations. These events, although perhaps underreported, were not clinically serious. The most common

ones were itching and a rash. Other effects (e.g., shortness of breath, gastrointestinal effects) occurred in a few patients.

Data on chronic human exposure to permethrin come primarily from studies of pest-control workers and clinical evaluation of patients treated for scabies and lice infestations. Data again support the conclusion that permethrin is extremely safe when used in conventional applications. Furthermore, reproductive studies do not show any attributable adverse impact from fairly high doses of permethrin. Animal studies of subacute and chronic exposure, even at high doses, generally fail to show any lasting effects. Only at extremely high doses do animals begin to demonstrate evidence of neurologic impairment.

We uncovered few references for *d*-phenothrin. Those that were available repeatedly address the relative safety of this insecticide and the pyrethroids in general. The effects of *d*-phenothrin on animals include acute toxicity but only at extremely high doses and in routes inconsistent with conventional exposure of humans. Similarly, studies of the chronic effects of *d*-phenothrin on animals show toxicity but only at extremely high oral doses. Even at these high exposures, reproductive, genetic, and carcinogenic effects were not observed. The literature does not provide evidence of *d*-phenothrin toxicity to humans.

Pyrethroids, particularly permethrin and *d*-phenothrin, are safe and effective when used in recommended applications. Studies show that these compounds are potentially toxic at extremely high exposures; however, when used in conventional ways, only minor skin irritation in sensitive individuals results, and the irritation subsides after short periods when the irritant is removed.

Organophosphates

Organophosphate Compounds. Organophosphate (OP) compounds were first synthesized in significant amounts during the 1940s, when tetraethylpyrophosphate was developed as an insecticide.

Azamethiphos is an OP pesticide that was probably procured locally during ODS/DS as a fly bait. It has been used in Canada, Scandinavia, the United Kingdom, and France to control sea lice infestations and in Mexico, primarily for fly control. Commercially available azamethiphos products include Alfacron 10 and Snip. Alfacron 10 is used as a wettable powder, and Snip is a 1 percent azamethiphos granular fly bait. Both were reported to have been used during ODS/DS, and both were probably obtained locally.

Chlorpyrifos is a broad-spectrum insecticide. It is registered for a variety of uses and sites and is effective in controlling cutworms, corn root worms, cock-

roaches, grubs, flies, termites, and fire ants. It is available in a variety of formulations, including granules, wettable powder, dustable powder, and emulsifiable concentrate.

Diazinon is an insecticide used to control cockroaches, silverfish, ants, and fleas in buildings. Diazinon is also commonly used in home gardens and on farms to control a wide variety of sucking and leaf-eating insects. It is available in dust, granules, seed dressings, wettable powder, and emulsifiable solution formulations.

Dichlorvos is effective against flies, aphids, spiders, and caterpillars. It acts against insects as both a contact and a stomach poison. Dichlorvos is used as a fumigant and has also been used to make pet collars and pest strips.

Malathion is a wide-spectrum insecticide. It is used to control sucking and chewing insects on fruits and vegetables and also to control mosquitoes, flies, household insects, and animal parasites. During ODS/DS, malathion was primarily intended for use as an outdoor spray to control mosquitoes and flies.

Potential Health Effects of Organophosphates. OP agents bind to and inhibit the normal action of acetylcholinesterase (AChE), an enzyme. Acetylcholine (ACh) is a major nerve-signaling chemical that acts as a chemical messenger both in the brain and elsewhere in the body. AChE serves a critical role in regulating nerve signaling to other nerve cells or to muscle cells. When AChE is inhibited by an OP, an excessive accumulation of ACh occurs in the synapse, followed by excessive binding of ACh to the receptors on the receiving cell. Consequently, cells are excessively stimulated.

In cases of toxicity from OP exposure, symptoms can range from mild tremors to more severe muscle contractions, impaired cognition, dizziness, shortness of breath, and vomiting. In severe cases, respiratory failure and death can result. Other effects include excess secretions (sweating, tearing, and salivation), bradycardia, miosis, insomnia and sleep abnormalities, headaches, dizziness, effects on mood (depression and anxiety), effects on personality (aggressiveness, irritability, and paranoia), effects on cognition (confusion, and enhancements and reductions in measures of attention, concentration, memory, learning, and psychomotor speed), tremor, ataxia, dysarthria, hypotension, respiratory depression or arrest, convulsions, and coma.

The severity of acute symptoms relates to the amount and route of exposure. There were no systematic reports in the literature of acute toxicity resulting from any pesticide exposures during ODS/DS. For this reason, this report focuses primarily on chronic exposures and long-term effects, as chronic health effects are of greater relevance to Gulf War illnesses.

As with other pesticides, most of what is known about the effects of persistent OP exposure in humans is based on observational studies. These studies are usually focused on occupational exposures, and they commonly involve a mixture of pesticides and possibly other compounds. Many of the studies involve assessing symptoms of a study group that is exposed to pesticides seasonally. Further, a combination of acute and chronic exposures and effects is often present, and this combination is usually undefined. Other knowledge is gained from case reports, many of which involve household pest control. These types of studies were reviewed for the reported ranges of chronic symptoms associated with OP exposure, including fatigue, joint and muscle symptoms, sleep effects, headaches, skin effects, cognitive effects (memory loss, confusion), mood effects, and neurological effects. These classes of symptoms are also seen frequently in ill PGWV.

Carbamates

Carbamate Compounds. The use of carbamates as insecticides began in the 1950s, and approximately 25 carbamate compounds are in use today as pesticides or pharmaceuticals. Carbamates are among the most popular pesticides for home use, both indoors and on gardens and lawns.

Bendiocarb is a broad-spectrum insecticide used to control disease vectors, such as mosquitoes and flies, and household and agricultural pests. Most formulations of bendiocarb are registered for general use, except for Turcam and Turcam 2.5G, which are restricted products. Perhaps the best known bendiocarb product is Ficam. Formulations include dusts, granules, ultra-low-volume (ULV) sprays, and wettable powders. Bendiocarb was primarily available during ODS/DS as a wettable powder for indoor surface treatment.

The EPA classifies *methomyl* as highly toxic to humans and restricts its use. Methomyl was introduced in 1966 as a broad-spectrum insecticide and was first registered in 1968. It was re-registered in 1998, with the U.S. EPA concluding that methomyl products did not pose unreasonable risk to humans or the environment when labeled and used correctly. Methomyl can be formulated as a wettable powder, a soluble concentrate or liquid, a dust, or a solid bait. It was intended to be used exclusively as a fly bait during the Gulf War.

Propoxur was introduced in 1959 as an insecticide, and it was first registered in the United States in 1963. Like methomyl, it has both contact and systemic activity against insects and is used on a variety of pests in both agricultural and other applications. Propoxur is a general-use pesticide, although some formulations may be for professional use only. Propoxur is characterized as having a fast knockdown and long residual effect, which makes it a popular choice for pest control. It is used primarily indoors, with limited outdoor applications.

Propoxur is available in a variety of formulations, including emulsifiable concentrate, wettable powder, dustable powder, granules, aerosol generator, smoke generator, and baits. During ODS/DS, propoxur (Baygon) was available to control pests in cracks and crevices (e.g., cockroaches) and could also be sprayed on building surfaces and screens to control pests outdoors.

Potential Health Effects of Carbamates. Carbamates have the same presumed primary mechanism of toxicity that characterizes OPs: They are AChE inhibitors. For this reason, OPs and carbamates are often considered together. But whereas OPs irreversibly inhibit AChE, requiring more enzyme to be produced for function to be restored, carbamates inhibit the enzyme reversibly. The body of literature regarding the acute and chronic effects of carbamates is largely covered in the discussion of OPs.

Symptoms found to occur following exposure to AChE inhibitors such as OP and carbamate pesticides include fatigue, joint and muscle symptoms, sleep effects, headaches, skin effects, cognitive effects, mood effects, and neurological effects. These classes of symptoms are also seen frequently in ill PGWV.

CONFOUNDING FACTORS

Part of the difficulty in evaluating possible effects of pesticides on PGWV is that a number of factors confound the evaluation. Primary among these are the inherent differences among individuals and potential interactions among pesticides and other influences, including drugs and the environment.

Individual Differences

A number of individual differences complicate the analysis of the effect of pesticides on PGWV. First, genetic differences occur among individuals. For example, DEET is potentially more toxic to people with genetic or acquired defects in ammonia metabolism, such as carriers of ornithine carbamoyl transferase (OCT) deficiency. Second, many factors may affect the rate and magnitude of pesticide absorption. Protective clothing and differences in skin properties and integrity influence dermal exposure, and inhalation exposure may vary with ventilation or as a result of other factors, including properties of airway membranes. Furthermore, the rates at which pesticides are cleared depend on amounts, genotype, and activity of enzymes involved in their metabolism. Some evidence points to differences in metabolizing enzymes among PGWV. Finally, individual differences in cofactors that modify the effect of pesticides, are essential for metabolism of pesticides, or permit or inhibit toxic effects by pesticides may contribute to differences in clinical effects. Such cofactors can include vitamins C and E, phytochemicals, and cholesterol.

Interactions

Pesticides in combination with other factors may exert effects different from those experienced with pesticides alone. Moreover, effects from two pesticides may differ from those expected from exposure to either separately. It is not feasible to predict the toxicity of pesticide mixtures (or pesticides in combination with other exposures) on the basis of the results of the toxicity of single compounds. Moreover, the number of possible combinations increases exponentially with the number of agents as 2^n; thus, 10 compounds have more than 1,000 possible combinations that could have different consequences. The effects of interactions may be additive, synergistic, or antagonistic, and the character of the interactions may differ for different effects of the compounds.

Nevertheless, it is possible that multiple exposures to pesticides and other compounds occurred during ODS/DS, underscoring the need to further investigate the nature of these potential exposures. Some data are available on interactions of substances relevant to ODS/DS, including interactions among DEET, pyridostigmine bromide (PB) (a carbamate drug given to protect against nerve agents), and pesticides; among pyrethroids, OPs, and carbamates; and among pesticides and drugs or other exposures.

DEET has been reported to enable other chemicals to penetrate the skin more easily. A scenario involving a soldier using DEET, wearing a uniform treated by permethrin, and taking PB is quite plausible. Data concerning the combination of DEET, PB, and pesticides show a greater-than-additive effect when two or three of the chemicals are present. However, the doses used in the studies of these combinations were exceptionally high. For example, in one study, a 160-pound subject would have to take 467 PB tablets and apply 76 tubes of a 33 percent DEET solution to achieve an equivalent exposure. These levels make it difficult to understand the implications for health effects at much lower levels. However, the increased effect demonstrated when the compounds are used in combination indicates that this phenomenon warrants further attention.

Effects on the ACh system constitute one mechanism by which interactions of pyrethroids with OP and carbamate pesticides may occur (other mechanisms of interaction are also possible). Some animal studies have found pyrethroids in the fat and brain of exposed subjects and in poisoned cotton sprayers, so the possibilities of interactions occurring even with a delay following pyrethroid exposure remain a concern.

One report on PB characterizes interactions between that carbamate and heat, stress, caffeine, nicotine, and antihistamines. Because other carbamates, as well as OPs, share PB's major pharmacological effect (AChE inhibition), the data on potential interactions with these agents also have bearing. The use of PB in

combination with an OP pesticide may have a novel effect on central ACh regulation.

Environmental factors also complicate the analysis of effects. Heat may affect the blood brain barrier, and it also affects acetylcholinergic nerve terminal function. It may increase the quantity of ACh released, potentially exacerbating the effect of AChE inhibitors. Antihistamines also have potential cholinergic effects, so interactions between antihistamines and OP/carbamate pesticide exposure might also be anticipated.

Other potential interactions of interest involve diet, alcohol, and diet supplements. Studies in rats have demonstrated that diet can affect susceptibility to the adverse effects of pesticides. Possible mechanisms of interaction among pesticides that relate to diet and alcohol intake include membrane effects. Because alcohol affects membranes, it cannot be excluded as an exacerbating factor. Studies have shown protective effects by antioxidant vitamins on lipid peroxidation and oxidative damage, which OP agents have been shown to cause; however, it should be noted that the dose of vitamin may determine whether it has primarily a prooxidant or an antioxidant effect.

CONCLUSIONS

A review of the scientific literature is but one step in determining the potential contributions of pesticides to the symptoms reported by some PGWV. Although it can assist in developing essential hypotheses, such a review cannot itself completely substantiate or repudiate a causal link between pesticide use and illness. To date, estimations of exposure and degree of PGWV illness have relied heavily on self-reported evidence, a method with several important limitations. It is hoped that this review will provide relevant information about the potential human health effects of pesticide exposure at levels reported in the literature, and that this information will be useful in subsequent efforts to further characterize the role, if any, of pesticides in Gulf War illnesses.

Where possible, the review focuses on reports in the scientific and medical literature that may be relevant to symptoms reported by some PGWV. There were no identified reports of acute exposure to pesticides that resulted in toxicity severe enough to cause PGWV to seek medical treatment during ODS/DS. The body of literature that is most informative therefore focuses on long-term, chronic human effects of reported pesticide exposures. Specific attention has been paid here to OP and carbamate pesticides, because the literature contains more breadth and depth in research and clinical findings related to the role of these AChE inhibitors in long-term, chronic effects, which are most relevant to Gulf War illnesses. The literature related to the other classes of pesticides lacks this robustness, in some cases due to a paucity of

research, but more often because long-term human effects have not been consistently observed.

The central question, of course, is whether the scientific literature suggests that pesticides could contribute to health problems reported by PGWV. Evidence in the literature is suggestive, but not conclusive, that pesticides, specifically AChE inhibitors such as OPs and carbamates, could be among the potential contributing agents to some of the undiagnosed illnesses seen in PGWV. Potentially supportive evidence exists in the areas of epidemiology, genetic and biological differences between ill and healthy subjects, physiological mechanisms of AChE inhibitors, and similarities between clinical findings of AChE inhibitor-exposed subjects and reported symptoms among PGWV. Clearly, significant uncertainties remain, especially in linking these lines of evidence with actual exposures to AChE inhibitors (including pesticides) during ODS/DS. It is also clear that more research is needed to confirm or refute a causal link between pesticides and other agents and illness among PGWV. No prospective studies have been conducted that positively identify pesticides as causative agents of the symptoms associated with Gulf War illnesses.

While further research can provide ever stronger evidence about the role of AChE inhibitors such as pesticides in the genesis of illness, such lines of inquiry may not provide independent identification of all the causes of illnesses in PGWV. This is especially true if several—or even many—causes of illness exist that are possibly interactive and manifested differently among individuals. Clearly, such approaches can be made more promising with increasing knowledge of actual exposure to potential causative agents, including pesticides, during ODS/DS.

Although the scientific literature has implicated exposure to AChE-inhibiting chemicals (including some pesticides) as a contributing factor in several well-defined conditions, including some health problems similar to some experienced by PGWV, few problems or symptoms are uniquely characteristic of pesticide exposure. Given the evidence to date and the literature reviewed, it is inappropriate to rely upon exposure to pesticides, especially OPs and carbamates, as the explanation for the myriad health problems reported by PGWV; however, we think it equally inappropriate at this point to completely rule out pesticides as a potential contributing factor. It is clear that more research will be necessary to further define any potential role that pesticides may have played in causing undiagnosed illnesses seen in PGWV.

ACKNOWLEDGMENTS

The authors would like to thank the Honorable Bernard Rostker, Special Assistant for Gulf War Illnesses (now Under Secretary of Defense for Personnel and Readiness), for sponsoring this work. We thank Jerry Sollinger, of RAND, who provided expert advice and assistance in organizing and writing this report. Roberta Shanman and Tomiko Envela, also of RAND, assisted us with the extensive literature search and deserve our gratitude. We thank the Entomological Sciences Program of the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) for their prompt assistance and for providing pesticide labels. We thank Terri Tanielian for assistance in managing the administration of this project and Jennifer Powell for assistance in editing this report. We are also indebted to Ron Fricker, of RAND, Stephen Roberts, of the University of Florida, Miriam Salpeter, of Cornell University, and Phillip Williams, of the University of Georgia, for their thorough reviews and comments, which substantially improved this report. However, the content and conclusions remain the sole responsibility of the authors.

ACRONYMS AND ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ACh	acetylcholine
AChE	acetylcholinesterase
AChEi	acetylcholinesterase inhibitors
AChEr	acetylcholinesterase receptors
AD	Alzheimer's disease
AFPMB	Armed Forces Pest Management Board
ALS	amyotrophic lateral sclerosis
AP	alkaline phosphatase
APT	Alexander Passalong test
ARCOM	U.S. Army Reserve Command
BBB	blood brain barrier
BDU	battle dress uniform
BuChE	butyrylcholinesterase
BVRT	Benton visual retention test
C	centigrade
CAS	Chemical Abstracts Service
CCEP	DoD Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CF(S)	chronic fatigue (syndrome)
CI	confidence interval, or Cornell Index
CNS	central nervous system
D1-D5	labels for 5 dopaminergic receptor transcripts
DA	dopamine
DNBI	disease and non-battle injury
ECG	electrocardiogram

EEG	electroencephalogram
EPA	U.S. Environmental Protection Agency (also USEPA)
FDA	Federal Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FM	fibromyalgia
FSRA	forced respiratory sinus arrhythmia
GGT	gamma glutamyl transpeptidase
GI	gastrointestinal
GNDS	general neuropsychological deficit scale
GUP	general-use pesticide
GWI	Gulf War illness
hr	hour(s)
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IDLH	immediately dangerous to life or health (value)
IOM	Institute of Medicine
Ip	intraperitoneal
IRIS	Integrated Risk Information Service (USEPA)
IV	intravenous
kg	kilogram(s)
L	liter(s)
LAP	leucine amino peptidase
lb	pound(s)
LC50 or LC_{50}	median lethal concentration
LD50 or LD_{50}	median lethal dose
LDH	lactate dehydrogenase
M1-M5	labels for 5 muscarinic ACh receptor transcripts
MCS	multiple chemical sensitivity
mg	milligram(s)
ml or mL	milliliter(s)
mM	millimolar
mm	millimeter(s)
MMWR	*Morbidity, Mortality Weekly Report* (published by CDC)
mo	month(s)

mPa	milliPascal(s)
MSA	multiple-system atrophy
msec	millisecond(s)
µg	microgram(s)
µL	microliter(s)
m^2	square meter(s)
m^3	cubic meter(s)
NA	not available
NBC	nuclear, biological, chemical
NCV	nerve-conduction velocity
ng	nanogram
NHL	non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NOEL	no observable effect level
NRC	National Research Council
NS	not significant
NSN	National Stock Number
NTE	neuropathy target esterase
OC	organochlorine
OCT	ornithine carbamoyl transferase
ODS/DS	Operations Desert Shield and Desert Storm
OP	organophosphate
OPIDN	OP-induced delayed neuropathy
OR	odds ratio
OSAGWI	Office of the Special Assistant for Gulf War Illnesses
OSHA	Occupational Safety and Health Administration
OSHAct	Occupational Safety and Health Act
PAI	personality assessment inventory
PB	pyridostigmine bromide
PCC	Poison Control Center
PD	Parkinson's disease
PEL	permissible exposure limit
PGW	Persian Gulf War
PGWV	Persian Gulf War veterans

p.o.	per os (by mouth)
PON	paraoxonase (also PON1)
POR	prevalence odds ratio
PP	preparkinsonism
ppb	parts per billion
ppm	parts per millionn
PR	prevalence ratio
PTSD	post-traumatic stress disorder
RA	resting heart-rate variability
RBC	red blood cell
REL	recommended exposure limit
RfC	reference concentration
RfD	reference dose
RR	relative risk
RUP	restricted-use pesticide
SCE	sister-chromatid exchange
SD	standard deviation
SGPT	serum alanine aminotransferase (also ALT)
SMR	standardized mortality ratio
SPECT	single photon emission computerized tomography
SSID	signs, symptoms, and ill-defined conditions
STEL	short-term exposure limit
TLV	threshold limit value
TPT	tactual performance test
TWA	time-weighted average
ULV	ultra-low volume (pesticide spray)
USAR	U.S. Army Reserve
USEPA	U.S. Environmental Protection Agency (also EPA)
USNG	U.S. National Guard
VA	Veterans Administration
WAIS	Wechsler adult intelligence scale
WHO	World Health Organization
wk	week(s)
WMS	Weschler memory scale
WRAT	wide-range achievement test

Chapter One

INTRODUCTION

A majority of the American military personnel who served during Operations Desert Shield and Desert Storm (ODS/DS)[1] were exposed to personal or field-use pesticides. Although toxicity may vary by individual, it is known that pesticides, when used improperly, can result in health problems that are similar to those experienced by some Persian Gulf War veterans (PGWV). This report examines the scientific literature pertaining to the health effects of pesticides available during ODS/DS as part of the ongoing effort to understand better the possible causes of undiagnosed symptoms among some PGWV.

The report is intended to be used in combination with two other studies undertaken to improve the understanding of pesticide exposures during ODS/DS. *Pesticide Use During the Gulf War: A Survey of Gulf War Veterans* (Fricker et al., 2000) reviews the findings of a survey of some 2,000 PGWV that attempts to quantify the use of pesticides during ODS/DS. *Pesticides Environmental Exposure Report*, being prepared by the Office of the Special Assistant for Gulf War Illnesses (OSAGWI), investigates the use of pesticides in the Gulf and the possible risk to troops who served there.

The present report reviews the scientific literature on 12 of the 35 pesticide active ingredients that were potentially used during ODS/DS.[2] OSAGWI asked RAND to focus on the potential health effects of these 12 compounds, which it considers to be of particular concern because of either toxicity or expected exposure. The compounds consist of five organophosphate (OP) pesticides

[1]While the terms *ODS/DS, Persian Gulf War (PGW)*, and *Gulf War* have been used interchangeably by some authors, including those of other volumes in this series, officials in the Office of the Special Assistant for Gulf War Illnesses consider that all personnel who served in the Kuwait Theater of Operations from August 1990 to July 1991 are veterans of ODS/DS. In this report, *ODS/DS* is usually used to refer to that theater of operations; however, *PGW* and *Gulf War* are also used, reflecting the literature reviewed. Similarly, the terms *Persian Gulf War veterans (PGWV)* and *Gulf War veterans* have become synonymous with *ODS/DS veterans* in much of the literature, and both will be found in this report.

[2]The review was originally intended to address 11 pesticides. Bendiocarb was added after completion of the first draft.

(azamethiphos, chlorpyrifos, diazinon, dichlorvos, and malathion), three carbamate pesticides (bendiocarb, methomyl, and propoxur), two pyrethroid pesticides (permethrin and *d*-phenothrin), one organochlorine pesticide (lindane), and one repellent (DEET). The report summarizes the relevant literature and then examines the possible links between known pesticide exposures or doses and related health outcomes.

BACKGROUND

Iraq invaded Kuwait on August 2, 1990. In support of United Nations Resolution 660, the United States responded by sending troops to the Persian Gulf in Operation Desert Shield. On January 16, 1991, Operation Desert Storm commenced with an air war against Iraq that was followed, 39 days later, by a four-day ground war. The Department of Defense (DoD) has estimated that nearly 700,000 American troops served in ODS/DS.

Many PGWV have reported an array of health problems.[3] The most commonly reported symptoms include joint pains, sleep disorder, memory loss, and fatigue. Studies show that these symptoms occur more frequently among PGWV than among persons who were not deployed to ODS/DS (Joseph, 1997). A variety of studies have characterized symptoms and diagnoses in PGWV, and their reported health problems are a source of continuing concern to veterans and policymakers. This concern has prompted efforts, including the present one, to evaluate whether exposures of these veterans to various risk factors during ODS/DS might be linked to their reported symptoms.

A review of military history reveals that disease and non-battle injury (DNBI) account for substantially more casualties than do battle wounds. DNBI prevalence and estimates of DNBI for future conflicts have decreased markedly in recent decades, largely due to the success of military preventive medicine practices. These essential practices include the use of pesticides to control pests that can carry and transmit diseases such as malaria or leishmaniasis. While the DNBI rate during ODS/DS was extremely low, the illnesses reported by veterans of that conflict and the absence of readily identifiable causes have led policymakers and health specialists to consider the very pesticides that ostensibly contributed to the preventive medicine success of ODS/DS as a cause of some illnesses.

METHODS

We conducted a systematic literature review in consultation with an experienced RAND librarian. This review included a detailed search of the following

[3]See Chapter Three.

databases: BIOSIS, CARL UnCover, CASearch, Chemical Abstracts, Chemtox, Embase, Medline, Scisearch, SilverPlatter Applied Science and Technology Index, and Toxline. The search terms included each of the pesticide classes (e.g., OP, carbamate) and each of the pesticides of concern (by name, synonyms, and Chemical Abstracts Service (CAS) registry number). The search also included various databases and data sources, such as those made available by the U.S. Environmental Protection Agency (EPA), state environmental agencies, and other organizations detailed in Chapter Two.

The initial search was restricted to English language articles or those with English language abstracts published between 1980 and 1998, inclusive. These dates were chosen because a search that did not restrict dates yielded more results than could be managed. The initial search resulted in over 7,000 titles. As the literature review progressed, references to articles published before 1980 were noted and such articles were retrieved as needed; articles published after 1998 were included as they became available. Articles and reports that appeared relevant based on titles resulting from this initial search were identified and accessed.

ORGANIZATION OF THE REPORT

Chapter Two provides general information about pesticides, including the history of and reasons for pesticide use, the taxonomy of pesticides, and the ways in which pesticide use is regulated in the United States. It also includes a brief discussion of the challenges of determining risk associated with pesticide use and the role this report may play in such a determination. What is currently known about pesticide availability and possible use during ODS/DS is also discussed in Chapter Two; however, the chapter does not report on specific pesticide exposures that were encountered during ODS/DS. Chapter Three discusses symptoms reported to be experienced by some ODS/DS veterans.

Chapters Four through Seven are organized by pesticide chemical class. Each deals with a specific class of pesticide and includes general information about the class, with subsections arranged by specific pesticides of concern. Each subsection includes information about the use and chemistry of a particular pesticide. Explanations of the types of information presented, including occupational health values, are included in Chapter Two. In addition, some pesticide subsections include unique information of specific interest to the study of Gulf War illnesses.

Following the specific pesticide subsections in each chapter is a review of the scientific literature related to the potential health effects of each class of pesticide. Chapters Four through Seven are generally organized in sections that present acute effects, chronic effects, genetic effects, reproductive effects, and carcinogenic effects. Exposures of animals or humans to chemicals are typically

classified into one of four categories: acute, subacute, subchronic, and chronic (Eaton and Klaasen, 1996, p. 15). Acute exposure is exposure to a chemical for less than 24 hours; usually, but not always, it refers to a single administration. Subacute exposure refers to repeated exposure for up to one month, subchronic for one to three months, and chronic for more than three months. Because not all authors use this classification scheme, we avoid strict divisions of the literature by including subacute and subchronic exposures in sections covering acute and chronic exposures, respectively. While *immediate* and *long-term* may be more appropriate as descriptors of effects, we use *acute* and *chronic* because this substitution is more prevalent in the reviewed literature. In this review, the above classifications are used where possible, but differing interpretations are recognized and stated.

The potential health effects of OP and carbamate pesticides are reviewed in a single chapter because of the toxicological similarities of these pesticide classes, as is further explained in the text. While the reviews of the potential health effects of each chemical are organized in a similar manner, there are also differences that reflect the nature of the literature.

Chapter Eight deals with confounding factors, such as interactions and individual differences, and Chapter Nine presents concluding remarks and suggests additional research.

Chapter Two

PESTICIDES

BACKGROUND

What Are Pesticides?

Pesticides are natural or synthetic agents that are used to kill unwanted plant or animal pests. While the term *pesticide* is now often associated with synthetic chemical compounds, it was not until relatively recently that synthetic pesticides came into use. Naturally occurring compounds or natural extracts have been used as pesticides since ancient times. The earliest pesticides were most likely salt, sulfurous rock, and extracts of tobacco, red pepper, and the like. It is rumored that the Napoleonic army used crushed chrysanthemums to control lice, with limited effectiveness. Petroleum oils, heavy metals, and arsenic were used liberally to control unwanted pests and weeds until the 1940s, when they were largely replaced for many uses by organic synthetic pesticides, the most famous of which is DDT.

Because the broad term *pesticide* encompasses a diverse collection of substances, an explanation of pesticide taxonomy and nomenclature is warranted. Pesticides can be classified either by target pest or by chemical identity.[1] Classification by target pest is perhaps the most familiar. For example, insecticides are pesticides that target insects, and herbicides target plants. There are many more examples (acaricides target ticks, nematocides target nematodes, etc.), but it is important for the purposes of this report to note that 11 of the 12 pesticides of concern identified by OSAGWI are insecticides and/or acaricides. The twelfth, DEET, is also directed against insects and ticks, but it is unique in that it is considered a repellent rather than an insecticide. To avoid confusion, the term pesticide is used in lieu of subclassification alternatives in this report.

[1]Certainly there exist other bases for classification, for example, by formulation (emulsions, powders, etc.) or by mode of toxic action (cholinesterase inhibition, etc.). However, target pest and chemical identity are most often used—and are frequently a source of confusion.

Pesticides can also be organized by their chemical class. A pesticide class is a group of pesticidal compounds that share a common chemistry. For example, all pesticides in the class organophosphate (OP) are derivatives of phosphoric acid, and all pesticides in the class organochlorine are composed of carbon, hydrogen, and chlorine. There are also chemical subclasses of pesticides, but these are beyond the scope of this discussion. This report considers four chemical classes of insecticides, as well as the repellent DEET, which is more conveniently identified by its mode of use.

When discussing a pesticide, it is possible to refer to the pesticidal compound itself or to the pesticide product or formulation. The compound itself is also known as the active ingredient—the chemical responsible for killing the target pest. The formulation is the manner in which the active ingredient is delivered. Typical formulations include liquids, dusts, wettable powders, and emulsifiable concentrates. The pesticide formulation includes the active ingredient as well as other ingredients. These other ingredients may be inert, such as talcum powder, or they can act to enhance the pesticidal properties of the active ingredient. For example, some pesticide formulations include a synergist that enhances the toxic activity of the active ingredient. Other ingredients in many pesticide formulations are solvents. When considering the potential health effects of pesticides, it is important to consider the toxicity of the active ingredient as well as the other ingredients in the formulation. This is often a daunting task. Clinical reports of pesticide poisoning provide clues about the toxicity of the pesticide formulation or product, while controlled experiments involving laboratory animals may include the formulation or just the active ingredient alone.

Pesticide Regulation

The EPA regulates both active ingredients and pesticide formulations under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[2] FIFRA gives the EPA the authority to regulate pesticides to ensure that their use does not have unreasonable adverse effects on humans and the environment. The registrant of a pesticide must submit specific data to the EPA to support the conclusion that the product meets this standard before the EPA will grant a registration that allows the pesticide to be marketed and sold. This can be a lengthy and expensive process. It includes approval of a pesticide label that provides information on the use and safety precautions related to the product. Under FIFRA, this label is legally binding. For example, it would be illegal to use a pesticide product in a food service establishment if the product is not specifically labeled for

[2]Despite its name, FIFRA governs all pesticides, not just those targeted against insects, fungi, and rodents.

that use. Following approval by the Armed Forces Pest Management Board (AFPMB), the U.S. military can procure pesticide products registered by the EPA and must follow the label instructions.

As part of the registration process, the EPA differentiates between general-use and restricted-use pesticides (GUPs and RUPs), primarily on the basis of EPA toxicity class. GUPs can be sold to the public for unrestricted use, while RUPs can be sold to and used only by certified applicators.[3] The distinction between GUPs and RUPs can be somewhat confusing, because the classification can refer to either the active ingredient or the formulation. For example, the inclusion of some active ingredients makes any pesticide product an RUP, while in other cases, the distinction between GUP and RUP is made by pesticide formulation. Consider two pesticide products containing the same active ingredient but different formulations. If the EPA does not consider all products with this active ingredient to be RUPs, one of those products can be for general use and the other restricted, because their formulations might be considered to present different risks to humans or the environment.

Related to the distinction between GUP and RUP on a pesticide label is the EPA toxicity class. This classification is based on acute human toxicity, hazard to applicators, and ecological effects. The acute human toxicity is assessed via animal tests, and ecological effects include the potential for groundwater contamination. Each toxicity class is associated with a signal word, which must appear on the pesticide label. The toxicity classes are shown in Table 2.1.

PESTICIDE IDENTITY AND PROPERTIES

Tables in Chapters Four through Seven present the identity and chemical and physical properties of each pesticide of concern. This information is intended to enable cross-referencing regarding the chemical identity of the pesticides as well to provide data that may be useful in characterizing their environmental behavior and potential health effects. References for these tables include the

Table 2.1

EPA Pesticide Toxicity Classes

Toxicity Class	Toxicity Rating	Signal Word on Label
I	Highly toxic	DANGER-POISON
II	Moderately toxic	WARNING
III	Slightly toxic	CAUTION
IV	Practically non-toxic	CAUTION

[3]Or in some cases, applicators directly under their supervision.

Merck Index (10th ed., 1983), the EPA Integrated Risk Information Service (IRIS) database (http://www.epa.gov/iris), the EPA Pesticide Product Information System Databases (http://www.epa.gov/opppmsd1/PPISdata/index.html), the EXTOXNET database,[4] and pesticide labels graciously provided by the Entomological Sciences Division of the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). Original references were obtained for verification. Occupational exposure values (standards and recommendations) were obtained from the American Conference of Governmental Industrial Hygienists (ACGIH, 1999);[5] reference doses and concentrations (RfD and RfC) were obtained from the IRIS database. In addition, Cheremisinoff and King (1994), Hornsby et al. (1996), and Kamrin (1997) provided references and directions to original sources.

The characteristics summarized in the physical and chemical properties tables for each pesticide of concern are described below.

Molecular Weight, Color, Form, and Odor. These entries are self-explanatory and are presented as the range of values reported in the referenced sources, where appropriate. The color, form, and odor of pesticides are generally restricted to the active ingredients and are given here because they may assist recall efforts of veterans being surveyed about their potential exposure to pesticides. It should be noted, however, that these values could be substantially different for pesticide formulations used during ODS/DS.[6]

Water Solubility. The water-solubility value is given for the active ingredient at room temperature, either 20°C or 25°C. Values are presented as milligrams of solute per liter of water (mg/L); in most cases, mg/L can also be reported as parts per million (ppm), even for very soluble compounds (Hornsby et al., 1996). Generally, the higher the value, the more readily the compound dissolves in water.

Partition Coefficient (K_{ow}). The octanol-water partition coefficient indicates how a chemical is distributed at equilibrium between organic (octanol) and aqueous (water) phases. This coefficient is primarily used in predicting the environmental fate of organic chemicals such as pesticides. The higher the coef-

[4]http://ace.ace.orst.edu/info/extoxnet. EXTOXNET is a cooperative effort of the University of California, Davis; Oregon State University; Michigan State University; Cornell University; and the University of Idaho. Primary files are maintained and archived at Oregon State University.

[5]This reference, published as a CD-ROM, includes the most recently published occupational exposure values from the ACGIH, the Occupational Safety and Health Administration (OSHA), and the National Institute for Occupational Safety and Health (NIOSH), and the carcinogenicity classifications given in this report.

[6]A separate, concurrent effort by RAND that surveyed some 2,000 PGWV addresses the formulations more specifically (Fricker et al., 2000).

ficient, the greater the propensity for the chemical to be partitioned to organic phases. This generally means that the chemical will tend to adhere to organic matter in the soil (e.g., organocolloids), but it may also indicate a tendency to accumulate in fat, although this behavior depends on other biological factors in the body. The partition coefficient is included in this report primarily because it is often used to estimate other chemical and physical properties.

Soil Sorption Coefficient (K_{oc}). This coefficient is sometimes called an adsorption coefficient. The distinction between adsorption and absorption is that the latter requires the movement of a chemical across a barrier such as tissue or a cell membrane. The soil sorption coefficient more accurately measures the chemical's propensity to "attach," or adsorb, to soil particles. The term *soil sorption coefficient* is used to avoid confusion. The utility of this measurement is that it assists in predicting whether a pesticide will remain dissolved in solution or will become adsorbed to soil particles after its application (or following a spill). If a pesticide is adsorbed to soil particles, it may be less available for biodegradation or for runoff or leaching. This assessment could be useful in estimating the potential for pesticide exposure. Generally, K_{oc} values below 500 indicate little or no adsorption of the pesticide to soil (indicating a high possibility of runoff or leaching).

Vapor Pressure. This value is given in millimeters of mercury (mm Hg), the unit of measure most often used. To convert to millipascals (mPa), one divides this value in mm Hg by 7.52×10^{-6} (Hornsby et al., 1996). Vapor pressure is a measure of the tendency of a pesticide to volatilize, a phase change that can affect estimations of exposure. Generally, the lower the vapor pressure, the lower the volatilization tendency of the chemical. Vapor pressure values are given for active ingredients of pesticides in this report.

EPA Toxicity Classification. The EPA toxicity classifications presented in this report were discussed above (Table 2.1).

ACGIH Threshold Limit Values–Time-Weighted Average (TLV–TWA). These values are developed by ACGIH as guidelines to assist in the control of health hazards and are not legal standards. TLVs refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects.[7] TLV–TWA represents these concentrations as the time-weighted average

[7]This definition is provided by ACGIH (1999), which explains that, "Because of wide variation in individual susceptibility . . . a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness. . . . Individuals may also be hypersusceptible or otherwise unusually responsive to some

concentration for a conventional eight-hour workday and a 40-hour workweek. Substances listed with the designation "skin" refer to the potential significant contribution to overall exposure by the cutaneous route. TLVs are based on available information from industrial experience and from experimental animal and human studies, and, when possible, from a combination of the three.

NIOSH Recommended Exposure Limits (REL–TWA, REL–STEL, and IDLH). These values are recommended by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC). Acting under the authority of the Occupational Safety and Health Act (OSHAct) of 1970 (29 USC Chapter 15) and the Federal Mine Safety and Health Act of 1977 (30 USC Chapter 22), NIOSH develops recommended exposure limits (REL) for hazardous substances or conditions in the workplace. The REL–TWA values are time-weighted average airborne concentrations for up to a 10-hour workday during a 40-hour workweek. Short-term exposure limits (REL–STEL) are 15-minute TWA exposures that should not be exceeded at any time during the workday. For most substances with a TLV–TWA, there is currently not enough toxicological information available to warrant a STEL, as evidenced by the limited availability of STELs reported here. IDLH values are concentrations that are immediately dangerous to life or health.

OSHA Permissible Exposure Limits (PEL–TWA). These regulatory limits are established by the Occupational Safety and Health Administration (OSHA) and have the force of law in occupational environments where OSHAct is applicable. PELs are also time-weighted averages and assume exposures of eight hours a day for a 40-hour workweek. PELs are based on human and animal studies, allowing for scientific uncertainty.

EPA Oral Reference Doses (RfD) and Inhalation Reference Concentrations (RfC). The RfD and RfC can be used to estimate a level of environmental exposure at or below which no adverse effect is expected to occur. The RfD or RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure that is likely to be without appreciable risk of deleterious effects to humans, including sensitive subgroups, over a lifetime. These values are based on lifetime exposure.[8]

Carcinogenicity. Carcinogenicity classifications are provided as reported by the ACGIH, the EPA, and the International Agency for Research on Cancer (IARC). These classifications are summarized in Table 2.2. They are generally

industrial chemicals because of genetic factors, age, personal habits (e.g., smoking, alcohol, or other drugs), medication, or previous exposures."

[8]http://www.epa.gov/iris/limits.htm.

Table 2.2

Carcinogenicity Classifications

Agency/Categories	Classification
ACGIH	
A1	Confirmed human carcinogen
A2	Suspected human carcinogen
A3	Confirmed animal carcinogen with unknown relevance to humans
A4	Not classifiable as a human carcinogen
A5	Not suspected as a human carcinogen[a]
EPA – 1986[b]	
A	Human carcinogen
B	Probable human carcinogen
B1 subgroup	Limited evidence from epidemiological studies
B2 subgroup	Sufficient evidence from animal studies; inadequate or no evidence from epidemiological studies
C	Possible human carcinogen
D	Not classifiable as to human carcinogenicity
E	Evidence of non-carcinogenicity for humans
EPA – 1996	
K	Known human carcinogen
L	Likely to produce cancer in humans
CBD	Cannot be determined
NL	Not likely to be carcinogenic in humans
IARC	
1	Carcinogenic to humans
2A	Probably carcinogenic to humans
2B	Possibly carcinogenic to humans
3	Unclassifiable as to carcinogenicity in humans
4	Probably not carcinogenic to humans

[a]The categories A4 and A5 can be confusing. The basic difference is that A4 substances cause concern that they could be carcinogenic for humans but cannot be assessed conclusively because of a lack of data; A5 substances are not suspected to be human carcinogens, based on human epidemiologic studies, or because the evidence suggesting a lack of carcinogenicity in experimental animals is supported by mechanistic data.

[b]As found in the 1986 *Risk Assessment Guidelines* (EPA/600/8-87/045). New guidelines for carcinogen risk assessment were proposed in 1996 (1996 *Proposed Guidelines for Carcinogen Risk Assessment*, Federal Register: 61[79]:17960-18011). These new guidelines were proposed due to advances in toxicological science. One significant limitation of the old guidelines is that a compound was considered carcinogenic if there was evidence of carcinogenicity from one exposure pathway, even in the absence of such evidence from other pathways. None of the pesticides of concern have been classified under the 1996 system; the old classifications are presented here for future comparisons.

based on the availability and weight of evidence of carcinogenicity from properly designed animal and human studies.

PESTICIDE USE IN ODS/DS

In every war and military conflict, combat effectiveness has been significantly reduced by disease, and a large number of diseases can be directly linked to

disease-carrying organisms such as arthropods and rodents.[9] Not only can these organisms transmit disease, their bites can result in distracting and demoralizing conditions and can cause serious secondary infections and allergic reactions. For these reasons, pest control is of significant military importance, affecting not only troop morale and welfare but also overall unit combat effectiveness and strength.

During ODS/DS, insects and rodents were of particular concern as potential disease vectors. The primary focus for pest management was on ground troops.[10] With roughly one-half million personnel deployed to the region in a very short time, under widely varying living, working, and threat conditions, this logistical challenge was large.

Pests of concern in the Persian Gulf region included arthropods such as sand flies, "filth flies," black flies, mosquitoes, cockroaches, lice, ticks, scorpions, spiders, and centipedes. These vermin are capable of transmitting major diseases such as viral encephalitis, malaria, sand fly fever, and leishmaniasis, as well as being an extreme nuisance because of their overabundance.[11] Rodents such as rats, mice, and voles were also of concern as disease vectors and contaminants of food supplies.

During ODS/DS, military authorities recommended various pesticides to control a variety of pests. The pesticides recommended for use by U.S. forces were listed by the AFPMB and approved for use by the EPA. Table 2.3 lists the pesticides used or potentially used by U.S. military units during ODS/DS. As detailed in Chapter One, OSAGWI has identified 12 pesticides that it considers to be of particular concern either because of toxicity or expected exposure; these pesticides are identified in bold type in Table 2.3.

More than 35 types of pesticides and pesticide products were used by military personnel during ODS/DS. None of the pesticides used was unique to the military; all are, or were at the time, legally available for civilian uses in the United States or other countries. When the provided quantities of pest-control products ran very low, purchases were made from the local economy in Saudi Arabia. For example, insecticide bait containing the active ingredient azamethiphos was reportedly purchased in Saudi Arabia and used by U.S. units. This

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[9] *Personal Protective Techniques Against Insects and Other Arthropods of Military Significance*, U.S. Army Technical Information Memorandum No. 36, Armed Forces Pest Management Board.

[10] Indigenous pests were not considered a significant threat to personnel remaining on naval vessels. It was expected that their exposure was no different from that of personnel afloat in any other part of the world; therefore, no special studies of that group have been performed.

[11] See note 9 above.

Table 2.3

Pesticides Used or Potentially Used During ODS/DS

Active Ingredient Product	Synonyms, Trade Names	Target Pests
Allethrin	d-trans-Allethrin	Insects
Aluminum phosphide	Phostoxin, Fumitoxin, AlP	Stored product pests
Amidinohydrazone	Combat	Insects
Azamethiphos	Snip Flykiller, Alfacron	Flies
Bacillus thurengiensis	Teknar	Mosquito larvae
Bendiocarb	Ficam W	Roaches, fleas, ticks, mosquitoes, other arthropods
Boric acid	Whitmire (PT 240) Perma-dust	Insects
Brodifacoum	Talon G	Rodents
Bromadiolone	Maki	Rodents
Carbaryl	Sevin	Ants, fleas, other insects
Chlorophacinone	Rozol	Rodents
Chlorpyrifos	Dursban	Mosquitoes, other insects, ticks, mites
Cypermethrin	Demon	Insects
Deltamethrin		Insects
Diazinon		Insects
Dichlorvos	DDVP,	Insects
Diethyl-*m*-toluamide	DEET, 3M Insect/Arthropod and Cutter Insect Repellents	Sand flies, other insects, ticks
Diphacinone	P.C.Q., Rodent Cake, Di-Blox	Rodents
Ethyl hexanediol		Insects
Lindane		Lice
Malathion		Insects
Methomyl	Flytek	Flies
Pentachlorophenol		Fungi
Permethrin	Permanone	Insects
Pet flea and tick collars	Amitraz, carbaryl, chlorpyrifos, methoprene, permethrin, phosmet, propoxur, tetrachorvinphos	Insects, ticks
***d*-phenothrin**		Insects
Pindone		Rodents
Propoxur	Baygon	Flies, roaches, other insects
Pyrethrum/pyrethrins	Pyrenone	Mosquitoes, flies
Resmethrin		Insects
Sulfur	Chigg-Away	Chiggers (mites)
Valone		
Warfarin	O-R-500, Rodex, Final, Erase	Rodents

Source: Provided by OSAGWI.

product, manufactured by Ciba Geigy, is not available in the United States.[12] Local firms provided pest control services in selected areas, and around some industrial camps they applied pyrethroid insecticides and malathion on

[12]CDR T. Wayne Gale, presentation at the 137th Armed Forces Pest Management Board Meeting, July 18, 1991. CMAT Control #1997269-0000-014.

portable latrines. The actual total usage of pesticides by U.S. forces during ODS/DS is unknown, but estimates for pesticides acquired within the military supply system have been made from records indicating the amounts sent to the Gulf region minus the amounts returned (see Fricker et al., 2000). Total usage does not include any pesticides in the possession of units at the outset of ODS/DS or pesticides acquired outside the military supply system. Thus, it does not include any pesticides acquired from the local economy or any that personnel obtained on their own—factors that could lead to underestimates of pesticide use. There is anecdotal information that some troops obtained pest-control products such as citronella candles from private sources. And some service members brought or had mailed to them unauthorized pesticides such as pet flea and tick collars that were designed to protect pets. During ODS/DS, a popular actor who visited the area advised the viewing audience of a television show to send these pet collars to U.S. service personnel.[13] Other practices could have led to overestimates of pesticide use. These practices include units keeping pesticides received during ODS/DS and returning them to their units' supply stocks rather than the supply system, and giving pesticides to coalition partners. Both practices would result in overestimations of pesticide use when the "supplies in minus supplies out" method of estimating is employed.

[13]CAPT Herbert T. Bolton, "Pesticide Use by U.S. Forces During Operations Desert Shield and Desert Storm," AFPMB Testimony to the National Institutes of Health Technology Assessment Workshop on the Persian Gulf Experience and Health, April 27, 1994.

Chapter Three

HEALTH PROBLEMS IN PGWV

The epidemiology of illness in PGWV is not the focus of this report and indeed is the subject of a separate RAND effort. This chapter provides a summary of some factors related to epidemiology, but it is in no way intended to be a complete review of the epidemiological data.

PGWV REPORT HEALTH PROBLEMS

Many PGWV (approximately 100,000) have participated in health registries through the Veterans Administration (VA) or DoD, and most of them report having health problems. A variety of studies have characterized their symptoms and diagnoses. Table 3.1 shows, as an example, the most frequent principal diagnoses in PGW registry personnel as of February 1997 (N = 74,653). The findings, while generally consistent, vary somewhat with the wording and category boundaries employed to define the symptoms and diagnoses.

SYMPTOMS IN PGWV

Findings reported here are taken from a single study of symptoms in PGWV (Roy et al., 1998); findings from other studies evaluating symptoms are qualitatively similar. "Signs, symptoms, and ill-defined conditions" (SSID) constituted the primary diagnosis for 17.2 percent of the veterans and the primary or secondary diagnosis for 41.8 percent.

Although the authors state that "more definitive, often psychological, diagnoses can be made by increasing the intensity of the evaluation and by multidisciplinary input," no evidence was provided that psychological diagnoses would be made on intensive scrutiny at a higher rate in PGWV than in non-PGW personnel, or in personnel without symptoms (or perhaps those for whom symptoms were falsely assigned to deal with the possibility that diagnoses may be made precisely because of illness reporting).

Table 3.1
Most Frequent Principal Diagnoses in PGW Registry Personnel, February 1997
(N = 74,653)

Symptom	Frequency (%)
No diagnosis	22.8
Missing diagnosis	5.1
Pain in joints	4.0
Complaint for which no diagnosis was made	2.7
Psychalgia	2.0
Other specified adjustment reaction	1.9
Depressive disorder, not elsewhere classified	1.8
Contact dermatitis and other eczema, unspecified cause	1.6
Asthma, unspecified	1.6
Lumbago	1.6
Essential hypertension	1.5
Migraine	1.5
Malaise and fatigue	1.4
Allergic rhinitis, cause unspecified	1.3
Unspecified sinusitis (chronic)	1.3
Other and unspecified non-infectious gastroenteritis and colitis	1.3
Osteoarthritis, unspecified	1.1
Sleep disturbance	1.0
Irritable colon	0.9
Alopecia	0.9
Anxiety states	0.8
Headache	0.7

Source: Roy et al. (1998).

COMMENT ON HEADACHE

Of the subjects who had a primary diagnosis of headache, 35 percent were categorized as migraine (classified as neurological), 38 percent as tension (classified as psychological), and 27 percent as ill-defined SSID (Roy et al., 1998). There was also wide variation in diagnosis by region, with migraine diagnosed in 23 percent to 50 percent of all veterans, tension in 19 percent to 48 percent, and SSID in 4 percent to 41 percent (Roy et al., 1998). Table 3.2 lists the symptoms in order of prevalence.

In those with a primary diagnosis of good health, prevalences were as shown in Table 3.3.

Symptom prevalence for those given a diagnosis other than SSID (Table 3.4) and those diagnosed with SSID (Table 3.5) is qualitatively similar, and roughly

Table 3.2
Symptom Prevalence as Primary and Any Diagnosis

Symptom	Primary Diagnosis (%)	Any Diagnosis (%)
Fatigue	26.8	30.3
Headache	14.5	21.3
Sleep disorders	11.7	19.0
Memory loss	9.9	16.9
Sleep apnea	7.4	5.5
Rash	3.8	5.7
Dyspnea	4.7	8.0
Chest pain	2.4	3.9
Digestive	1.8	2.6

Source: Roy et al. (1998).

Table 3.3

Symptom Prevalence in Subjects with a Primary Diagnosis of Good Health

Symptom	Percentage
Fatigue	20.7
Joint pain	20.1
Headache	12.5
Sleep disturbance	11.2
Memory loss	14.7
Problems concentrating	9.2
Rash	10.9
Depressed mood	7.1
Muscle pain	6.7
Diarrhea	6.7
Hair loss	5.9
Dyspnea	4.9
Abdominal pain	5.3
Bleeding gums	3.6

Source: Roy et al. (1998).

similar in ordering, to that of other reports on symptoms in ill PGWV. Results from other studies are not reviewed here.

INCREASED SYMPTOM REPORTING IN PGWV

Many of the problems reported by ill PGWV also occur in the general population. It is desirable to know whether and to what degree PGWV experience higher rates of illness than others. Several studies have shown that those deployed to the Gulf have higher rates of self-reported physical symptoms

Table 3.4

Symptom Prevalence in Subjects Given a Diagnosis Other Than SSID

Symptom	Percentage
Fatigue	47.1
Joint pain	55.7
Headache	41.7
Sleep disturbance	34.6
Memory loss	35.6
Problems concentrating	27.9
Rash	32.2
Depressed mood	24.0
Muscle pain	23.7
Dyspnea	20.7
Diarrhea	19.2
Abdominal pain	17.9
Hair loss	13.2
Bleeding gums	9.1
Weight loss	7.2

Source: Roy et al. (1998).

Table 3.5

Symptom Prevalence in Subjects Diagnosed with SSID

Symptom	Percentage
Fatigue	59.5
Joint pain	47.4
Headache	44.3
Sleep disturbance	41.0
Memory loss	40.6
Problems concentrating	31.1
Rash	29.8
Depressed mood	21.5
Muscle pain	21.5
Dyspnea	20.2
Diarrhea	18.0
Abdominal pain	15.6
Hair loss	13.0
Bleeding gums	8.5

Source: Roy et al. (1998).

than those who were not deployed (Centers for Disease Control and Prevention, 1995; Stretch, 1995; Iowa Persian Gulf Study Group, 1997; Canadian Department of National Defence, 1998; Fukuda et al., 1998; Wolfe et al., 1998). Symptoms commonly reported by deployed veterans are those that might be expected from the diagnoses: fatigue, joint pain and stiffness, diarrhea, un-

refreshing sleep or sleep difficulties, diarrhea and abdominal discomfort, weakness, cognitive symptoms (e.g., difficulty remembering, problems with word finding, or impaired concentration), headaches, and weakness. Some recent efforts have been made to devise case definitions. One researcher has articulated case definitions for each of three syndromes identified by factor analysis (Haley, 1997). Another working definition requires symptoms in two of three major categories of fatigue, musculoskeletal symptoms, and mood-cognition (Fukuda et al., 1998).

The CDC conducted a study that evaluated symptoms in an Air National Guard unit from Pennsylvania (Unit A) and three comparison units from Pennsylvania and Florida chosen for similarity in mission responsibility (Centers for Disease Control and Prevention, 1995). A total of 3,927 personnel from four units participated in a survey, with response rates from 36 percent to 78 percent. In all units, the prevalence of each of 13 chronic symptoms (lasting six months or more) was significantly greater among subjects deployed to the Gulf than among those not deployed. The symptoms most frequently reported and considered "moderate" or "severe" included fatigue (61 percent), joint pain (51 percent), nasal or sinus congestion (51 percent), diarrhea (44 percent), joint stiffness (44 percent), unrefreshing sleep (42 percent), excessive gas (41 percent), difficulty remembering (41 percent), muscle pain (41 percent), headaches (39 percent), abdominal pain (36 percent), general weakness (34 percent), and impaired concentration (34 percent). The prevalence of five symptom categories—diarrhea, other gastrointestinal (GI) complaints, difficulty remembering or concentrating, "trouble finding words," and fatigue—was significantly greater among those deployed from Unit A than among those from the other units. Both self-report and selective participation could have biased these results, however.

A second, more complete evaluation of the cohorts examined by the CDC entailed a cross-sectional survey of 3,273 currently active volunteers from four Air Force units (including 1,155 PGWV and 2,520 non-deployed personnel), together with a cross-sectional clinical evaluation of 158 PGWV from one unit, irrespective of health status (Fukuda et al., 1998). A working case definition was determined in which criteria were satisfied for a case if one or more chronic symptoms were present from at least two of three categories: fatigue, mood-cognition, and musculoskeletal symptoms. Severe cases were those in which there were "severe" symptoms from each category. A factor-derived case was defined as one in which the combined factor score was in the top 25 percent of questionnaire responses, including those of non-PGWV. Forty-five percent of PGWV and 15 percent of non-deployed personnel were symptom-category cases. Forty-seven percent of PGWV and 15 percent of non-deployed personnel were factor-score cases. This suggests that the authors selected the 25 percent

cutoff to match the symptom-derived cases. The authors stated that the syndrome should be such that it embraces at least 25 percent of PGWV, but this is at once arbitrary and inappropriate: 25 percent of legionnaires or Four Corners residents would obviously not need to be ill for Legionella pneumonia or hantavirus to have produced an illness syndrome in those groups. For symptom-derived cases, 39 percent of PGWV and 14 percent of non-deployed personnel met criteria for mild to moderate illness; 6 percent vs. 0.7 percent met criteria for severe illness. Illness was reportedly not associated with time or place of deployment or with duties during ODS/DS. There were no differences in lifetime reports of 35 medical and psychiatric conditions, including heart disease, hypertension, diabetes, alcohol and substance abuse, anorexia/bulimia, migraine or severe headache, anxiety, diarrhea, irritable bowel syndrome, or impotence. History of prior depression was significantly more common in severe cases (15 percent) than in non-severe cases (0 percent, $p < 0.05$). Severe illness was associated with Gulf War service, female sex, enlisted rank, and smoking, on multivariate analysis. There was no association between illness and number of deployments, month/season of deployment, duration of deployment, military occupational specialty, direct participation in combat, or self-reported locality in the Gulf region (most of the respondents had been in Riyadh).

The Iowa Persian Gulf Study Group (1997) assessed the prevalence of self-reported symptoms in Iowa PGWV and non-deployed personnel. Of 238,968 persons, 4,886 were randomly selected from one of four groups: Gulf-deployed active-duty military, Gulf-deployed National Guard/Reserve, non-Gulf-deployed active-duty military, and non-Gulf-deployed National Guard/Reserve. A total of 3,695 subjects completed a telephone interview. Symptom reporting was higher for Gulf-deployed veterans for fibromyalgia (19.2 percent vs. 9.6 percent), cognitive dysfunction (18.7 percent vs. 7.6 percent), alcohol abuse (17.4 percent vs. 12.6 percent), depression (17 percent vs. 10.9 percent), asthma (7.2 percent vs. 4.1 percent), anxiety (4.0 percent vs. 1.8 percent), bronchitis (3.7 percent vs. 0.8 percent), post-traumatic stress disorder (PTSD) (1.9 percent vs. 0.8 percent), sexual discomfort (1.5 percent vs. 1.1 percent), and chronic fatigue (1.3 percent vs. 0.3 percent).

Another group distributed 16,167 survey questionnaires, of which 31 percent were returned; PGWV reported significantly more of each of 23 physical health symptoms than non-deployed veterans, an effect not significantly altered by controlling for smoking and drinking, age, rank, education, marital status, and branch of military service (Stretch et al., 1995, 1996a,b).

A study of exposures and symptoms in PGWV from a Fort Devens ODS Reunion Survey did not include a non-deployed control group but found that the five

most commonly reported symptoms among the 2,119 subjects who returned the survey (of 2,313 surveyed) were aches/pains, lack of energy, headaches, insomnia, and feeling nervous/tense (Wolfe et al., 1998). PTSD was associated with health symptoms, but subjects with combat exposure were not more likely to report increased health symptoms.

A survey was sent to all Canadian PGWV and a sample of those serving elsewhere during the Gulf War, a total of 9,947 personnel. The survey, returned by 3,113 PGW-deployed (73 percent of those solicited) and 3,439 non-deployed (60.3 percent), found that PGWV reported higher prevalences of symptoms of chronic fatigue, cognitive dysfunction, multiple chemical sensitivity, major depression, PTSD, anxiety, fibromyalgia, and respiratory diseases (bronchitis and asthma together) (Canadian Department of National Defence, 1998). It also found higher numbers of children with birth defects (before, during, and after the PGW).

Because these studies are based on self-reported illness, it is possible that reporting bias and self-selection could have influenced results. Although the degree to which these factors may influence self-reported symptomatology is unknown, it can by no means be assumed that bias serves as the sole explanation for the higher rates of symptom reporting by personnel deployed to the Persian Gulf.

FACTORS ASSOCIATED WITH REGISTRY PARTICIPATION

Determination of what constitutes the cause or causes of illness may be helped by analysis of factors associated with illness development. Registry participation is not equivalent to illness, since many PGWV who have not participated in registries report health problems, and some who have participated in registries report no health problems. However, a rough relationship between illness and registry participation is present. Table 3.6 shows predictors of registry participation and their associated odds ratios (Gray, 1996).

The degree to which predictors of registry participation predict illness as opposed to inclination to participate can be determined only by evaluating these predictors against more definitive criteria for illness. Indeed, some studies cite increased participation of reservists, who in one account represented nearly half of those reporting health problems, while making up only 17 percent of the troops serving in the PGW (Thompson, 1996). However, "the Pentagon attributes this discrepancy to the reluctance of active-duty soldiers to complain for fear of losing their jobs in a shrinking military, on the reservists' greater age and on the fact that the war disrupted their lives more severely than those of active-duty troops" (Thompson, 1996).

Table 3.6
Registry Participation Predictors

Factor	Odds Ratio
Stationed in PGW theater	2.2
Age: younger than 31/older than 22	2.1
Enlisted	2.0
Construction worker	1.3
Female	1.3
Hospitalized during 12 months prior to PGW	1.2
Army	4.7 (4.6–4.9)
National Guard	2.6 (2.5–2.6)

Source: Gray (1996).

INFORMATION FROM EPIDEMIOLOGICAL INVESTIGATIONS OF SELF-REPORTED PESTICIDE EXPOSURE AND ILLNESS

No definitive link has been found between self-reported pesticide exposure and illness in PGWV. Two factors have complicated determination of such a link: Both outcome data and information on exposures have been poor. Some information from epidemiological studies is available, and this information is consistent with the possibility of a link between self-reported pesticide exposure and illness, although it does not prove a causal connection.

Epidemiological studies performed on members of a Naval Reserve construction battalion (CB24) reported to have a high rate of PGW-attributed symptoms were surveyed for symptoms and for exposures. Three primary syndromes were identified, which were termed Syndrome 1 (impaired cognition), Syndrome 2 (confusion ataxia), and Syndrome 3 (arthro-myo-neuropathy). Syndrome 1 was correlated with the use of pesticide-containing flea and tick collars and pesticide applications in encampments ($p < 0.001$), and Syndrome 3 was related to heavy use of military-supplied insect repellent (DEET, 75 percent in ethanol) ($p < 0.001$) (Haley and Kurt, 1997a,b; Kurt, 1998). In addition, Syndrome 2 was correlated with chemical alarms ($p < 0.001$) and being in a sector later suspected to have potential nerve-agent exposure ($p < 0.04$). The provisos associated with self-report suggest that there may be increased recall of an exposure by those who are ill; however, there is no cogent rationale for presuming that these different syndromes would be systematically and differentially linked to these exposures (with one syndrome leading to amplified recall of one exposure, and another to amplified recall of a different exposure). If these relationships are preserved in a replication sample, this would provide credence to a possible link between pesticides (potentially including OPs) and Syndrome 1.

Another report found that among British servicemen (findings for men only were reported), service in the PGW was associated with increased incidence of

illness (using a description of an "empiric multisystem syndrome" for Gulf War illnesses [Fukuda et al., 1998]) based on comparisons with Bosnia and non-deployed PGW-era cohorts: an odds ratio of 2.5 (2.2 to 2.8) (Unwin et al., 1999). Among PGW, Bosnia, and PGW-era cohorts, 61.9 percent, 36.8 percent, and 36.4 percent met the working PGW illness criteria, respectively, with 25.3 percent, 11.8 percent, and 12.2 percent meeting criteria for severe symptoms. As shown in Table 3.7, various self-reported exposures were associated with illness in PGWV. In particular, self-reported exposures to pyridostigmine bromide (PB) and pesticides by British veterans were associated with increased odds ratios for the empiric multisystem syndrome of chronic, multisymptom, ill-defined illness. While the odds ratios for personal pesticide use and pesticides on clothes/bedding were high among the factors examined, it is interesting that these odds ratios are comparable for the three study groups for these and all other exposures examined. Recall and reporting bias remain possibilities, and many other exposures were also apparently associated with likelihood of illness.

In summary, many PGWV report health problems, and there is some consistency in the health problems reported among PGWV cohorts. Further, reporting of health problems occurs at a higher rate among PGWV than among other veterans. Self-reported exposures, including those to pesticides, in the PGW are associated with increased likelihood of illness. The likelihood that this is the result of recall bias in ill veterans is reduced by information showing that comparable odds ratios are seen for risk factors for which records are available for

Table 3.7
Odds Ratios for CDC-Defined PGW Illnesses in PGWV and Bosnia and Non-Deployed Gulf-Era Veterans (95 percent confidence interval)

Factor	PGW Veterans	Bosnia Veterans	PGW-Era, Non-deployed
PB	2.6 (2.2–3.1)	3.4 (1.7–6.8)	1.9 (1.4–2.8)
Pesticides on clothes or bedding	1.9 (1.6–2.2)	1.7 (1.4–2.2)	1.9 (1.5–2.3)
Personal pesticides	2.2 (1.9–2.6)	1.8 (1.5–2.2)	1.8 (1.5–2.2)
Exhaust from heaters or generators	1.9 (1.6–2.2)	2.8 (2.1–3.7)	2.4 (1.9–2.8)
NBC suits	2.7 (2.3–3.3)	2.7 (1.6–4.8)	2.3 (1.5–3.7)
Anthrax vax	1.5 (1.3–1.7)	1.5 (0.7–2.9)	NA
With records	1.4 (1.0–1.8)	2.6 (0.9–7.4)	NA
Any biological	1.5 (1.3–1.7)	1.5 (0.8–2.8)	NA
With records	1.4 (1.1–1.9)	2.5 (0.9–6.6)	NA
Yellow fever	1.3 (1.1–1.7)	1.0 (0.7-1.4)	NA
With records	1.4 (0.9–2.0)	0.8 (0.5-1.2)	NA
Tetanus	1.3 (1.1–1.5)	1.0 (0.8-1.3)	NA
With records	1.1 (0.8–1.4)	1.0 (0.7-1.3)	NA
Any routine	1.2 (1.1–1.4)	1.1 (0.9–1.3)	NA
With records	1.0 (0.7–1.3)	1.0 (0.7–1.3)	NA

NA = not available.

some (British) veterans. However, there is insufficient evidence to clearly define a causal link between self-reported pesticide exposure and increased likelihood of illness. If the existence of such a link is to be adequately examined, it will be necessary to conduct studies with replication samples of those reviewed above. There is also a need for more detail regarding health effects experienced by PGWV. The broad categories of effects in many current surveys often do not permit a determination of whether the symptoms can be logically associated with particular agents, such as pesticides, with or without more complete exposure data. Until more information is available on the symptoms and their context, the value of the surveys in terms of identifying a causal agent (or agents) will always be limited.

Chapter Four

LINDANE

GENERAL INFORMATION

Lindane belongs to the organochlorine (OC) pesticide class. This is one of the oldest classes of pesticides, and few OCs are still in use today. OC pesticides are so named because they include carbon, hydrogen, and chlorine. There are three major subclasses of OC pesticides: diphenyl aliphatics, cyclodienes, and hexachlorocyclohexane (HCH). The well-known pesticide DDT belongs to the first class. The HCH subclass is not so much a class as the collection of the five isomers of HCH: alpha (α), beta (β), gamma (γ), delta (δ), and epsilon (ε). Only the gamma isomer has insecticidal properties. This is the isomer manufactured as lindane.[1] Lindane has not been produced in the United States since 1977, but it is imported in multiple forms for pharmacologic and industrial use. The use of lindane is restricted by the EPA; it can be applied only by certified pesticide applicators.

Lindane production involves the purification of technical grade HCH (16 percent α-HCH, 7 percent β-HCH, 45 percent γ-HCH) to a 99.8 percent pure product. The α-HCH and β-HCH isomers (which have a half-life of seven to eight years) are metabolized, but γ-HCH is metabolized much faster (its half-life is less than one day); therefore, most metabolites recovered in urine are from the gamma isomer (i.e., lindane). The most common human metabolites observed are 2,3,5-trichlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, and 2,4-dichlorophenol (Angerer et al., 1983).

Lindane has been used to control a wide variety of insect pests in agricultural, public health, and medicinal applications. It is available as a suspension, emulsifiable concentrate, fumigant, seed treatment, wettable and dustable powder,

[1]This report focuses on exposure to lindane because this is the compound to which PGWV may have been exposed.

and ultra-low-volume (ULV) liquid. The chemical identity of lindane is shown in Table 4.1, and Table 4.2 summarizes its physical and chemical properties.

Table 4.1

Chemical Identity of Lindane

Characteristic	Information
Chemical class	Organochlorine
Chemical name[a]	γ-1,2,3,4,5,6-hexachlorocyclohexane
Trade names	Agrocide, Ambrocide, Aparasin, Aphatiria, Benesan, Benexane, BoreKil, BorerTox, Exagama, Gallogama, Gamaphex, Gammalin, Gamma-Col, Gamene, Gamiso, Gammex, Gammexane, Gamasan, Gexane, Isotox, Jacutin, Kwell, Lindafor, Lindaterra, Lindatox, Lorexane, New Kotol, Noviagam, Quellada, Steward, Streunex, Tri-6, Viton
Chemical formula	$C_6H_6Cl_6$
CAS Registry number	58-89-9

[a]Lindane (HCH) has historically and widely been inappropriately referred to as benzene hexachloride (BHC). This compound should not be confused with hexachlorobenzene (HCB) (Kamrin, 1997).

Table 4.2

Physical and Chemical Properties of Lindane

Property	Information
Molecular weight	290.85
Color/form	Colorless to white crystalline powder/solid
Odor	Odorless to slight musty or aromatic odor
Water solubility at 25°C	Insoluble
Partition coefficient (K_{ow})	5,248
Soil sorption coefficient (K_{oc})	1,100
Vapor pressure at 20°C	9.4×10^{-6} mm Hg
EPA toxicity classification	Class II
ACGIH TLV–TWA	0.5 mg/m^3 (skin)
NIOSH REL–TWA	0.5 mg/m^3 (skin)
NIOSH REL–STEL	NA
NIOSH IDLH value	50 mg/m^3
OSHA PEL–TWA	0.5 mg/m^3 (skin)
EPA IRIS RfD	3×10^{-4} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A3
EPA	NA
IARC	2B

NA = not available.

AVAILABILITY AND RECOMMENDED USE OF LINDANE DURING ODS/DS

Lindane dust was recommended for use during ODS/DS exclusively as a delousing agent, so the primary route of potential exposure in veterans was dermal; the secondary route was inhalation. Two lindane products were shipped to the Gulf; these are detailed in Table 4.3.

POTENTIAL HEALTH EFFECTS OF LINDANE

Lindane Metabolism/Pharmacokinetics

The effects of lindane are primarily neurotoxic and are similar to those of DDT, but lindane generally produces a more rapid response, especially in increasing insect respiration to lethal levels, for which it was designed. As with most OC pesticides, lindane interferes with fluxes of cations across nerve cell membranes, increasing neuronal irritability and producing convulsions. These convulsions may result in death by interfering with pulmonary gas exchange and by generating severe metabolic acidosis (Cheremisinoff and King, 1994).

Neurologic effects of lindane exposure have been attributed to alteration of sodium conduction in nerve axons (MacPhail et al., 1999) and on the picrotoxin binding site of the GABA-A receptor complex in the central nervous system (CNS) (Artigas et al., 1988; Suanol et al., 1988). This GABA-A-antagonist property impairs the inhibitory tone GABA exerts on CNS neurons (Artigas et al., 1988; Suanol et al., 1988).

Lindane and its metabolites can be detected and measured in blood and body fluids by clinical laboratory tests. But although lindane can be quantified, it is difficult to derive with certainty specific exposure levels based on measured blood and tissue levels. Further, although lindane metabolites are measurable,

Table 4.3

Formulations of Lindane Available During ODS/DS

National Stock Number (NSN)	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-00-242-4217	Lindane	Dust	1	2-oz can	Treat clothing; emergency use only
6840-00-242-4219	MIL-I-11490E	Dust	1	25-lb can	Treat clothing; emergency use only

Source: Provided by OSAGWI.

other environmental compounds, particularly chlorobenzene, produce the same metabolites.

Lindane has been widely used for about 50 years as an insecticide on crops and in medicinal formulas to treat head lice and scabies, so there exists a fair amount of data on its efficacy, safety, and toxicity (Parent-Massin et al., 1994). The primary routes of exposure are dermal absorption, ingestion, and inhalation.

Acute Effects

Dermal Exposure. Dermal exposure is an important consideration when evaluating lindane toxicity because of lindane's therapeutic use as a scabicide in creams and lotions and its use as a delousing agent during the Gulf War. Lindane is efficiently absorbed through human skin (Feldman and Maibach, 1974; Ginsburg et al., 1977). Hosler et al. observed a rise in plasma lindane from nondetectable levels to 10.3 ng/mL three days after dermal application of a 1 percent solution (Hosler et al., 1980).

Studies by Dick et al. demonstrated differential absorption depending on the vehicle (solvent) in which lindane is dissolved (Dick et al., 1997a,b). When an acetone formulation was used, the peak absorption period varied from three to 45 hours in volunteers; however, when white spirit (a commercial wood preservative) was used, the peak occurred more reliably, at 6.5 ±1.6 hours, and absorption was about twentyfold greater (Dick et al., 1997a). Animal studies confirm that ^{14}C radiolabeled lindane in acetone is effectively absorbed, with 18 percent, 34 percent, and 54 percent absorption of a dose applied topically to the forearm, forehead, and palm of rhesus monkeys (Moody and Ritter, 1989). A similar evaluation in rats showed 31 percent absorption following mid-dorsal application.

Animal studies substantiate the acute effects of lindane following dermal exposure. Rabbits given a single application of 1 percent lindane (total = 60 mg/kg) exhibited hyperexcitability, seizures, and convulsions (Hanig et al., 1976). Younger animals were more sensitive to the compound than their older counterparts. Ullmann (1986a) reported sedation for 24 hours in rats with a single applied dose of 1 g/kg. Repeated application of lindane to rats (0.18 mg lindane/kg 15 times over 25 days) produced a mild dermatitis (Dikshith et al., 1973), although a single application of 132 mg/kg to rabbits for four hours failed to produce toxicity (Ullmann, 1986c). Blood levels exceeding 20 ng/mL have been associated with neurologic effects (Czegledi-Janko and Avar, 1970; Dick et al., 1997a).

Death has been well documented in animals exposed to high doses of lindane. The LD_{50} for dermal exposure[2] in rats appears to be approximately 500 to 1,000 mg/kg (Gaines, 1960; Ullman, 1986a). In an accident, 10 grams of lindane were sprayed on each of 30 Charolais calves (300 kg) (Venant and Sery, 1991). The calves quickly showed muscular twitching, incoordination, and salivation. Two died one day after exposure, two died the following week, and a fifth died at five months. At 17 days, blood lindane in the surviving calves was measured at 130 ng/mL, dropping 70 percent between day 17 and day 56.

The literature contains several reports (most of them single cases) of human toxicity following dermal application of lindane, generally because of misapplication of a 1 percent solution. Illustrative cases are described in Table 4.4.

In 1996, the U.S. Food and Drug Administration (FDA) required manufacturers of lindane for pharmacologic use to caution consumers about the potential adverse consequences of misuse. The FDA acknowledged that the compound is safe and effective when appropriately used, but lindane treatments are often misused for several reasons. First, because dermal irritation persists for some period following parasite elimination, patients (and parents, in the case of children) may confuse continued pruritis with continued or repeated infestation. Some may also overtreat in an attempt to expedite symptom resolution. In general, the FDA recommends that other treatments be used except in patients who have failed those treatments or who are unable to tolerate them.

Oral Exposure. The clearest evidence of lindane toxicity comes from experimental and observational studies following oral exposure. Animal studies show neurologic and reproductive effects following acute exposure (Table 4.5). Young rats fed subconvulsant levels of lindane following birth exhibited clear behavioral changes (Rivera et al., 1998). Lindane readily crosses the placenta of Wistar rats, with concentrations being particularly high when exposure occurs later in gestation as fetal fat content increases (Khanna et al., 1991).

The literature contains a number of cases of accidental human lindane ingestion, primarily by adults who did not understand the method of treatment or by infants; there are also cases of individuals ingesting lindane intentionally. The most common acute manifestations include neurologic findings, particularly seizure, in addition to tremor, depressed mental status, vomiting, and coma. The first case shown in Table 4.6 was a 43-year-old female who intentionally ingested eight ounces of a 20 percent lindane solution. She developed a diffuse intravascular coagulopathy (DIC) that improved as serum lindane levels de-

[2] LD_{50} is the median lethal dose. This is a statistically derived single dose that can be expected to cause death in 50 percent of test animals when administered by the route indicated. It is expressed as the weight of a substance per unit weight of animal.

Table 4.4

Reports of Acute Lindane Toxicity in Humans Following Dermal Application

Reference	Age of Subject	How Applied	Blood Level	Manifestations
Boffa et al., 1995	18 yr	Three consecutive daily treatments	50 ng/mL at 2 days, 10 ng/mL at 4 days	Dermatitis and drowsiness at second application, grand mal seizure after third application. Condition resolved without residual findings.
Davies et al., 1983	2 mo (child born premature)	To abdomen and legs for 2 days, then entire body, left on for 18 hours	33 ng/mL	Death. This is the only case of death found from a dermal application of lindane.
Fischer, 1994	24 yr	Two treatments over 1 hour (1.5 times recommended dose) to excoriated skin areas	3 ng/mL 20 hr following the exposure	Visual hallucinations, involuntary movements. Returned to baseline 48 hours following symptom onset.
Pramanik and Hansen, 1979	Premature infant	Not stated	17 times greater than expected following a single dose	Seizures and abnormal neurologic findings.
Telch and Jarvis, 1982	18 mo	Two consecutive nights after hot bath	450, 80, and 29 ppb at 12, 24, and 96 hr, respectively	Seizure lasting 30 minutes 12 hours following second application. Disoriented, lethargic and restless, with tonic-clonic movements. Recovered.
Derek, 1984	23 yr	Applied to entire body one time, second application 1 wk later	Not reported	Tired, weak, and dizzy with imbalance and slurred speech at 12 hours after first application, clearing 12 hours later. After second application, loss of consciousness three times. Recovered after 24 hours.
Shuster, 1996	9 yr	Applied 3 times over 6 days, left on 10–15 min	Not reported	Severe headache, confusion. Recovered completely at 3 days.

Table 4.5

Reports of Acute Lindane Toxicity in Animals Following Oral Exposure

Reference	Animal Model	Concentration and Duration	Effect
Tilsonet al., 1987	Fischer-344 rats	15 mg/kg; or 30 mg/kg	Behavioral: decreased avoidance responses early; impaired passive avoidance retention at 7 days with 30 mg/kg dose.
Rivera et al., 1998	Wistar rats, immature	20 mg/kg single dose; or 10 mg/kg for 7 days	Behavioral: passive avoidance behavior improved with both dosings. The single dose decreased motor activity; the 7 day dosing increased motor activity.
Llorens et al., 1989	Wistar rats	10 mg/kg; 20 mg/kg or 30 mg/kg	Neuromuscular: decreased spontaneous behavior following exposure. Minimally effective dose determined to be 1.85 mg/kg.
Saxena et al., 1986	ITRC-bred albino rats (female)	20 mg/kg; gestation days 6 through 14	Reproductive: no significant fetal abnormalities with lindane alone. When lindane was combined with cadmium, there was significant decrease in body weight, increased embryonic deaths, and increased skeletal deformities.
Dalsenter et al., 1996	Wistar rats (male)	6 mg/kg for 5 days; or 30 mg/kg single dose	Reproductive: reduced spermatid and spermatozoa with histologic evidence of seminiferous tubule damage. Testicular toxicity not accompanied by overt evidence of toxicity.
Sircar and Lahiri, 1989	Swiss mice (female)		Reproductive: hormone deficiency (correctable with estrogen/progesterone) leading to reproductive and developmental failure.
Camaon et al., 1988	Rats	30 mg/kg single dose; or 10 mg/kg for 7 days	Metabolic: single dose induced hypothermia, particularly in the setting of cold stress (approximately –0.5°C). The lower, longer dose did not have this effect.

Table 4.6

Reports of Acute Lindane Toxicity in Humans Following Oral Exposure

Reference	Age of Subject	Blood Level	Time Since Ingestion	Manifestations
Sunder et al., 1988	43 yr	1.3 µg/mL	12 hr	Seizure, rhabdomyolysis, diffuse intravascular coagulopathy, death.
Starr and Clifford, 1972	2.5 yr	0.84 µg/mL	2 hr	Seizure.
Davies et al., 1983	16 yr	0.206 µg/mL	Approx. 2 hr	Seizure, coma. Regained function.
Munk and Nantel, 1977	35 yr	0.6 µg/mL	NA	Seizure, myonecrosis, pancreatitis.
Daerr et al., 1985	16 yr	0.25 µg/mL	Unknown	Lethargy, resting tremor.
Dale et al., 1966	NA	0.29 µg/mL	6 hr	Seizure.
Kurt et al., 1986	41 yr	1.3 µg/mL	First day	Death.
Burton et al., 1991	32 yr	0.13 µg/mL	< 2 hr	Vomiting, seizure (pt on phenytoin).
Aks et al., 1995	13 mo	0.32 µg/mL 0.02 µg/mL	4 hr 20 hr	Generalized tonic-clonic seizure. Improved over next few days.
Aks et al., 1995	2 yr	0.26 µg/mL 0.02 µg/mL	18 hr 39.5 hr	Vomiting, petit mal seizure. Improved.
Aks et al., 1995	16 mo	0.012 µg/mL 0.003 µg/mL 0.002 µg/mL	3 hr 7.5 hr 21 hr	Drowsiness.

creased. Despite the improvement in her coagulation profile, she died 11 days following ingestion.

On the basis of limited clinical data, Aks et al. (1995) concluded that lindane follows a two-phase pattern, with the first (distribution) phase having a short, two- to three-hour half-life and the second (elimination) having a longer, 35-hour half-life (range = 11 to 83 hours). Most individuals with acute oral exposures to lindane suffer the types of effects shown in Table 4.6. However, within a short period of time following metabolism of lindane (hours to days), their function returns to baseline without identified residual impairment.

Inhalation and Environmental Exposure. Few studies focus on acute effects of aerosol or environmental exposure of animals to lindane. Ullmann (1986b) exposed Wistar rats to lindane aerosol for four hours, then observed them for the

following three weeks. The study estimated that the LC_{50} was 1,560 mg/m^3.[3] In a subsequent study, exposing CD-1 mice to 10 mg/m^3 five days per week for six hours per day resulted in 16 percent mortality one week after exposure (Klonne and Kintigh, 1988).

Acute human exposure has resulted from accidents either in the manufacture of lindane or in its application in agricultural settings. Acute symptoms in humans exposed to lindane include headache, nausea, vomiting, restlessness, ataxia, tremor, and excitability (Solomon et al., 1977; Brassow et al., 1981). Seizure has been reported with more extensive exposures, although specific levels at the time of exposure are not available. (Czegledi-Janko and Avar, 1970; Mayersdorf and Israeli, 1974)

Chronic, Reproductive, Genetic, and Carcinogenic Effects

Dermal Exposure. Few studies specifically evaluate the effects of chronic dermal exposure to lindane, because the intended use of lindane for treating parasitic infection generally requires only a single application. However, in one study, female rats (Crl:(WI)BR) exposed to 10 mg/kg/day of lindane for 13 weeks (five days per week, six hours per day) exhibited hyperactivity, and those exposed to 60 mg/kg/day demonstrated ataxia and tremors (Brown, 1988). In the same study, mild renal impairment was observed, particularly in male rats exposed to 10 mg/kg/day.

A few studies document human hematologic manifestations, including bone marrow hypoplasia and aplastic anemia, following prolonged dermal exposures to lindane (Woodliff et al., 1966; Vodopick, 1975; Rauch et al., 1990). In vitro studies suggest that hematopoietic precursors, specifically Colony Forming Unit–Granulocyte and Macrophage (CFU–GM), are sensitive to lindane, and human precursors are more sensitive than those of the rat (Parent-Massin et al., 1994).

Oral Exposure. A number of animal studies provide insight into the potential effects of intermediate and chronic oral exposure to lindane (Table 4.7). Most studies focus on the neurologic and reproductive effects following such exposure.

We did not find definitive studies addressing chronic oral exposure to lindane in humans. Although such exposure could result, for example, from consump-

[3] LC_{50} is the median lethal concentration. This is a statistically derived concentration of a substance that can be expected to cause death in 50 percent of test animals. It is usually expressed as the weight of a substance per weight or volume of water, air, or feed.

Table 4.7

Reports of Chronic Lindane Toxicity in Animals Following Oral Exposure

Reference	Animal Model	Concentration and Duration	Effect
Banerjee et al., 1996	Hissar albino mice	10 ppm, 30 ppm, or 50 ppm for 12 wk	Immunologic: decreased primary humoral immune response at 12 wk for those exposed to the 50-ppm concentration; decreased secondary immune response starting at 3 wk for those exposed to 50 ppm, after 12 wk for those given 30 ppm. No overt signs of toxicity were observed.
Beard et al., 1997	Mink (female)	1 mg/kg/day for 3 wk before breeding, then followed for 8 wk (to weaning)	Reproductive: decreased acceptance of mating after 1 wk (decreased estradiol, reduced sexual receptivity). Whelping rate decreased but number of implantation sites was not impacted. Lindane increased embryo mortality (post-implantation loss), frequently due to loss of complete litters. No overt toxicity exhibited.
Chakravarty et al., 1986	Ducks (female)	20 mg/kg daily for 8 wk; or 20 mg/kg 3 times/wk for 8 wk; or 20 mg/kg 2 times/wk for 8 wk; or 20 mg/kg daily for 8 wk followed by stilbesterol; or 20 mg/kg 3 times/wk for 8 wk followed by stilbesterol	Reproductive: cessation of egg-laying for a period of time, followed by decreased egg-laying. Histology showed undifferentiated follicles but absence of mature vitellogenic and post-ovulatory follicles. Stilbesterol led to resumed egg-laying. Lindane reduced estradiol, reducing yolk protein synthesis.
Lahiri and Chakraborty, 1991	Ducks (female)	20 mg/kg daily for 8 wk; or 20 mg/kg 3 times/wk for 8 wk; or 20 mg/kg twice weekly for 8 wk	Reproductive: decreased serum calcium and calcium in the shell gland, particularly at higher doses. Shell thinning stemming from decreased shell formation and decreased mineral.
Arisi et al., 1994	Wistar rats (male)	1,000 ppm for 90 days	Neurologic: tonic convulsions.
Gilbert, 1995	Long-Evans rats (male)	10 mg/kg for 30 days; or 10 mg/kg 3 times/wk for 10 wk	Neurologic: increased behavioral sensitivity over time, persisting for 4 wk without additional dosing. Accelerated electrical kindling (development of behavioral seizures with repeat initially subthreshold stimuli). These findings were not accompanied by overt toxicity.
Llorens et al., 1992	Wistar rats (male)	10 mg/kg, 6 days/wk, for a total of 25 doses	Neurologic: increased spontaneous motor activity (about 30%) but no other changes (e.g., activity counts over 23 hr) 2 wk after exposure.
Wolff et al., 1987	F-1 hybrid mice (female)	160 ppm for 6, 12, 18, or 24 months	Neoplastic: different phenotypes showed different prevalence for clara cell hyperplasia and various (e.g., lung, liver) adenomas, and hepatocellular carcinoma.
Rivett et al., 1978	Beagle dogs	25, 50, or 100 ppm for 2 years; or 200 ppm for 32 weeks	Neurologic: minor EEG changes were observed with the 200-ppm exposure. GI: liver color appeared darker with the 100- and 200-ppm exposures but not with the 50-ppm exposure. No other adverse effects were observed.

tion of low levels of the pesticide in contaminated food products or from breast feeding (Ladodo et al., 1997; Al-Saleh et al., 1998), reported cases of lindane ingestion focus on acute accidental or intentional ingestion.

Inhalation and Environmental Exposure. There are few animal studies of chronic aerosol, vapor, or environmental lindane exposure. One study of CD-1 mice exposed to a lindane dust aerosol six hours per day, five days per week, reported a 22 percent mortality rate with exposure of 5 mg/m^3 for up to 20 weeks and a 2 percent mortality rate when the exposure was reduced to 1 mg/m^3 (Klonne and Kintigh, 1988).

Several reports discuss human exposure to lindane as an environmental toxicant. Lindane has been used in vaporizers and included among other chemicals in wood preservatives, as well as in agricultural settings. Individuals employed in the manufacture of lindane are also exposed; however, as discussed previously, these individuals are exposed to a combination of HCH isomers with different effects in biological systems (Baumann et al., 1980; Angerer et al., 1983). Some situations have precipitated unintentional prolonged exposures to low levels of lindane in the environment. Reports in the literature are either anecdotal or of an epidemiologic case-control nature, where subjects may have been exposed to a number of chemical toxicants simultaneously, making it difficult to attribute specific effects to individual chemical exposures.

Brassow et al. compared the health status, including laboratory parameters, of 60 German males employed in a plant producing lindane to that of 20 male clerks not so exposed (Brassow et al., 1981). The exposed individuals exhibited some statistical differences in laboratory parameters (i.e., increased neutrophil percent, decreased lymphocyte percent, increased reticulocyte counts, longer prothrombin times, and decreased serum creatinine and uric acid). Other laboratory variables, including total white cell count, standard urinalysis analytes (i.e., protein, glucose, urobilinogen), and liver enzymes, were not statistically different between the groups. No overt signs of toxicity were observed.

Cantor et al. studied agricultural exposure to 23 insecticides used on animals, 34 insecticides used on crops, 38 herbicides, and 16 fungicides, comparing exposed and non-exposed individuals to assess the risk of non-Hodgkin's lymphoma (Cantor et al., 1992). Table 4.8 summarizes their observations.

These findings suggest an increased lymphoma risk among farmers exposed before 1965 or not using protective clothing or equipment. Another case-control study of midwestern Caucasian men showed a similar association (Blair et al., 1998). However, it is again difficult to interpret individual pesticide risks because of multiple exposures, and because so many substances were studied simultaneously, the chance of spurious association with some is increased.

Table 4.8

Comparison of Exposures to Agricultural Chemicals Resulting in Risk of Non-Hodgkin's Lymphoma

	Ever Handled		Handled Before 1965	
Application	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
Lindane used as an animal insecticide	1.4	1.0–2.1	1.7	1.1–2.7
Lindane used as a crop insecticide	2.0	1.0–3.7	2.2	1.0–4.7
With use of protective equipment	2.0	1.0–3.7	—	—
Without use of protective equipment	—	—	2.6	1.2–5.5

In a limited study of 22 patients meeting the CDC definition of chronic fatigue syndrome (CFS) (Holmes et al., 1988), 17 patients with CFS symptoms but with a toxic exposure excluding them from the strict definition of CFS, and 34 control subjects, lindane was not detected in subjects (Dunstan et al., 1995). However, the incidence of other OC contamination (e.g., hexachlorobenzene) was statistically more likely to be present in those with CFS.

Several studies in the literature address the impact of environmental exposure to toxic substances, including lindane, on human reproduction (Saxena et al., 1980; Karmaus and Wolf, 1995; Gerhard et al., 1998). A German study assessed reproductive outcomes among female teachers exposed to wood preservatives in a daycare center (Karmaus and Wolf, 1995). Pregnancies in exposed women ended more frequently in induced or spontaneous abortions or in caesarian sections. Live births had reduced birth weights and infant body lengths comparable to those of infants whose mothers were not exposed; however, the study could not control for paternal factors. In addition to lindane, these teachers were exposed to pentachlorophenol (PCP) and trace amounts of other chemicals formed during the preservative production process. Saxena et al. also observed an association between OC levels in blood and placental tissue and premature labor and abortion (Saxena et al., 1980).

An Israeli study detected a statistically significant correlation between OC and polychlorinated biphenyl concentrations and the presence of oligospermia, defined as sperm counts below 20 million/mL (Pines et al., 1987). The control group (fertile males) had a mean lindane level of 1.13 ng/g serum (median 0.9 ng/g), whereas infertile males had a mean lindane level of 2.28 ng/g (median = 1.15 ng/g).

Another study examined the psychological impact of chronic exposure to wood-preserving chemicals known to contain lindane and PCP (Peper et al., 1999). Fifteen German women identified from a large number of individuals seeking care at a women's health center had been exposed to these chemicals

for at least five years (mean = 10 years). There were statistically significant differences in blood lindane and PCP levels of exposed women compared with those of unexposed controls. Using a series of psychological profile instruments, the investigators also found statistical differences in subjective complaints (i.e., attenuated motivation, fatigue, distractibility, and depressed mood) and memory parameters (e.g., verbal memory span, working memory, visual short-term retention, verbal fluency) among the individuals with pesticide exposure.

SYNTHESIS

Lindane is a well-known and extensively studied pesticide that is generally considered safe when used as directed.

Acute exposure precipitates neurologic changes including hyperexcitability, tremor, and coma. Many of these abnormalities are reversible with supportive care. However, deaths have been reported following lindane ingestion. In two of these cases, the victims had blood levels exceeding 1 μg/mL.

Epidemiologic studies in the literature suggest the possibility of subtle long-term neurologic and reproductive health effects; however, subjects in these studies were exposed to a number of different potentially toxic substances, making it difficult to attribute findings specifically to lindane.

Because of the potential risks associated with lindane, its use is no longer recommended as the first-line drug therapy for treating scabies and body lice. Although individuals should use lindane with caution, when used appropriately, it is generally considered a safe and effective pesticide.

Chapter Five

DEET

GENERAL INFORMATION

N,N-Diethyl-*m*-toluamide, also known as DEET or *m*-DET, is an aromatic amide that is an effective insect repellent for control of biting flies, biting midges, black flies, chiggers, deer flies, fleas, gnats, horse flies, mosquitoes, no-see-ums, sand flies, small flying insects, stable flies, and ticks. DEET was first developed by the U.S. Department of Agriculture for military use in 1946 and was first registered in the United States in 1957. It has been estimated that approximately 38 percent of the U.S. population uses DEET-containing repellents annually (Veltri et al., 1994; Selim et al., 1995). As of September 1998, 225 DEET products were registered with the EPA; they are prepared in many different application types (e.g., aerosol and non-aerosol sprays, creams, lotions, sticks, foams, and towelettes) and have DEET concentrations ranging from approximately 4 percent to 100 percent (USEPA, 1998a).

Technical DEET is composed of more than 95 percent *m*-DET isomers. Ortho (*o*-DET) and para (*p*-DET) isomers are slightly more and less toxic than *m*-DET, respectively (Ambrose and Yost, 1965). The chemical identity of DEET is shown in Table 5.1, and Table 5.2 summarizes its physical and chemical properties.

Table 5.1

Chemical Identity of DEET

Characteristic	Information
Chemical class	Aromatic amide (*N,N*-dialkylarylamides); repellent
Chemical name	*N,N*-Diethyl-*m*-toluamide
Trade names	DEET, OFF, Delphene, MGK diethyltoluamide, Detamine, Metadelphene, Chemform, Chiggar-Wash, Muskol, Cutter, Repel, Old Time Woodsman
Chemical formulas	$C_6H_4CH_3CON(C_2H_5)_2$ $C_{12}H_{17}NO$
CAS Registry number	134-62-3

Table 5.2

Physical and Chemical Properties of DEET

Property	Information
Molecular weight	191.26
Color/form	Colorless to off-white, light-yellow, amber liquid
Odor	Nearly odorless
Water solubility at 25°C	Practically insoluble
Partition coefficient (K_{ow})	100
Soil sorption coefficient (K_{oc})	300
Vapor pressure at 20°C	5.6×10^{-3} mm Hg
EPA toxicity classification	Class III
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	NA
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	D
IARC	NA

NA = not available.

AVAILABILITY AND RECOMMENDED USE OF DEET DURING ODS/DS

DEET insect repellent is part of a complete repellent system used by U.S. military personnel that has shown excellent efficacy in preventing arthropod-borne disease (Young and Evans, 1998). Until 1989, the standard-issue insect repellent of the U.S. military consisted of 75 percent DEET in an alcohol base. By 1984, the 3M Company (St. Paul, Minnesota) had developed a slow-release, polymer-based product containing 33 percent DEET, which is now the repellent provided to all U.S. military personnel. This product is available to the general public from 3M as Ultrathon. Three DEET products were shipped to the Gulf area; these products are detailed in Table 5.3.

Table 5.3

Formulations of DEET Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Areas
6840-01-284-3982	3M insect/arthropod repellent	Cream	33	2-oz tube	Skin and clothing
6840-00-753-4963	Insect repellent, clothing and personal application	Liquid	75	2-oz bottle	Skin and clothing
6840-00-142-8965	Cutter insect repellent stick	Stick	33	1-oz stick	Skin and clothing

Source: Provided by OSAGWI.

POTENTIAL HEALTH EFFECTS OF DEET

DEET Metabolism/Pharmacokinetics

Carbon dioxide and lactic acid are among the most important cues mosquitoes use to locate a host. It is believed that DEET repels mosquitoes by inhibiting lactic acid receptors on their antennae (Davis and Sokolove, 1976).

DEET can enter the body through several exposure pathways, including dermal and ocular exposures, inhalation, and ingestion. Some consider DEET an ideal permeant of skin (Stinecipher and Shah, 1997), and it has been reported to accelerate the dermal penetration of pharmaceuticals (Windheuser et al., 1982), raising the concern that DEET may also increase dermal penetration of pesticides, since they are often used together (Moody et al., 1987). Several studies in animals and humans have shown that, following absorption, DEET is completely metabolized prior to elimination in the urine (Schmidt et al., 1959; Smith et al., 1963a; Selim et al., 1995).

After DEET is applied to the skin, it is partially absorbed, but some also evaporates[1] or is rubbed off by clothing, the latter accounting for the majority of loss (Smith et al., 1963b). Following absorption, DEET does not appear to accumulate in the superficial layers of the skin. In a definitive study, DEET was absorbed across the forearms of human volunteers within two hours of application, but the rate of elimination via excreta was more rapid than the rate of absorption (Selim et al., 1995). This is consistent with expected absorption patterns of low-molecular-weight, lipophilic chemicals (Scheuplein, 1967) such as DEET.

DEET has been shown to affect the cardiovascular and nervous systems. The mechanism of cardiovascular toxicity has been investigated in dose-response experiments with intraperitoneal injections of DEET in rats, studies of hypodynamic responses of dogs following intraperitoneal DEET injections, and studies of the effect of atropine in blocking DEET-induced hypotension and bradycardia (Leach et al., 1988). These experiments showed a significant effect of hypotension. In the dog study, there was a significant reduction in cardiac output but no change in stroke volume and total peripheral resistance, suggesting that the observed hypotension was a result of DEET-induced bradycardia.

Episodes of severe DEET toxicity in mammals are usually related to a direct action on the nervous system. Experimental animals that received large doses of DEET have manifested coma and death. Animal studies have suggested that

[1]There is some evidence, however, that there is little or no evaporation of DEET from the skin of rats (Schoenig et al., 1996) and humans (Selim et al., 1995).

DEET is not a selective neurotoxin (Osimitz and Grothaus, 1995; Schoenig et al., 1996).

Reported cases of severe DEET toxicity in humans have involved mainly encephalopathies in children. The vast majority of these cases occurred in female children exposed to topical DEET, so it was hypothesized that another mechanism of DEET toxicity that may occur with smaller systemic doses is perturbation of ammonia metabolism (Heick et al., 1988), resulting in hyperammonia. In this case, DEET would be especially toxic to individuals with genetic or acquired defects in ammonia metabolism, such as female carriers of ornithine carbamoyl transferase (OCT) deficiency (this condition is usually fatal in neonatal males). Heick et al. (1988) injected normal mice with DEET and observed acutely increased ammonia levels. While this result, as reported in case-study observations, suggests hyperammonia as a primary mechanism of acute DEET toxicity, the authors also point out several cases that suggest hypersensitivity reactions (Miller, 1982; Roland et al., 1985). Furthermore, cases of DEET-associated seizures in boys (MMWR 1989; Lipscomb et al., 1992) and men (MMWR, 1989; Veltri et al., 1994) may discredit the hypothesis that OCT deficiency is the predisposing factor for DEET CNS toxicity (Lipscomb et al., 1992), or may at least suggest that there is yet another responsible mechanism.

Exposure to DEET as Reviewed in the Scientific Literature

It is beyond the scope of this literature review to speculate about the magnitude of exposures to pesticides by individuals during ODS/DS. However, Robbins and Cherniack (1986) provide some exposure information that may prove useful. It should first be noted that limited information is available for estimating exposure from what these authors refer to as "conventional consumer use practices." Table 5.4 presents predictions based on limited mid-range data points for DEET exposure (USEPA, 1980). Robbins and Cherniack (1986) rightfully point out that considerable error may be associated with some of the estimates, which were made during the mosquito season and reflect 60 applications per year for military personnel and four days of use per week for Everglades biologists—the latter intended to represent high-dose use. It should also be noted that military personnel were using the old 75 percent DEET repellent. Although this formulation was available in limited quantities during ODS/DS, a 33 percent DEET extended-duration formulation was the primary DEET repellent used there. Robbins and Cherniack also included data from the preliminary report of a NIOSH Health Hazard Evaluation, based on survey data of Everglades Park Service employees. These data are not presented in Table 5.4 because of their preliminary nature and the fact that they included a range of DEET concentrations (15 percent to 75 percent) applied for a seven-month period (as opposed to six months in the EPA study). Nonetheless, this

Table 5.4

Estimated Exposure to DEET During a Six-Month Mosquito Season

Group	Concentration *of DEET in Formulation* (%)	Estimated Exposure to Active Ingredient Reported	Exposure Quantity[a] (g)
Upper 1% of general population[b]	15	> 1.65 g/day	>214
	75	> 8.35 g/day	>1071
Military personnel	75	43 g/season[c] *(approximately 0.12 g/day)*	43
Everglades biologist[d]	28.7	4.25 g/day	442

Source: U.S. EPA (1980), in Robbins and Cherniack (1986). Italics indicate additions in the present report.

[a]Exposure quantity is estimated and assumes the active ingredient is applied to all exposed skin during May to October.

[b]Estimated from a survey of only 71 employees of one company.

[c]Annual exposure is based on the U.S. Army's estimated usage of 1 ml of a 75 percent formulation, 60 times per year.

[d]Exposure based on four-day use per week.

evaluation calculated an estimated exposure of >2 kg of DEET over seven months, which can be approximated as 9.5 g/day. The EPA provides some additional estimates of exposure to DEET, calculated assuming one application per day and standard body weights: 12.10 and 9.68 mg DEET/kg/day (USEPA, 1998a).

Skin Permeation and Absorption of DEET

Uncertainty about the degree of percutaneous absorption of DEET in humans complicates an objective assessment of effects. Generally, the amount of DEET that permeates the skin is closely related to the repellent formulation. Using commercially available products, Stinecipher and Shah (1997) found that the cumulative amount of DEET that permeated human skin in vitro ranged from approximately 6 percent to 100 percent, depending upon the repellent tested. Earlier research suggested that approximately 9 percent to 56 percent of applied DEET permeates the skin, although only approximately 15 percent is systematically absorbed (Robbins and Cherniack, 1986). However, in vitro studies involving infinite-dose applications of DEET to human skin have agreed closely: Stinecipher and Shah calculated the steady-state flux of DEET at from 21 to 63 $\mu g/cm^2/hr$ (Stinecipher and Shah, 1997), while Moody et al. calculated it to be from 20 to 60 $\mu g/cm^2/hr$ (Moody et al., 1995).

To determine DEET absorption accurately, it is necessary to recover all applied DEET, achieving mass balance. Few studies have been successful in this approach. One study that reports good mass balance (88.7 percent to 94.3 percent

of radioactivity from ^{14}C-labeled DEET accounted for, depending upon formulation applied) is that of Selim et al. (1995). In this study, ^{14}C-labeled DEET formulations of 100 percent and 15 percent in ethanol were applied to the forearms of two groups of six human volunteers. After eight hours, the skin was washed, and samples were taken by applying tape to the skin at one, 23, and 45 hours after rinsing. Serial blood, urine, and stool samples were also analyzed, and radioactivity was used as the marker to estimate biodistribution of DEET. Plasma radioactivity indicated absorption of DEET within two hours of application, but elimination was rapid and was complete four hours after the eight-hour exposure period. Most of the DEET was washed off the skin, and most of that which was absorbed was metabolized: Six major metabolites were observed in the urine, the primary route of excretion. These results definitively refute earlier suggestions (Bloomquist and Thorsell, 1977; Spencer et al., 1979; Snodgrass et al., 1982; Stinecipher and Shah, 1997) that the epidermis may serve as a depot for DEET, with subsequent slow release to the circulation. Based upon the percentage of applied DEET recovered in the total excreta, dermal absorption of DEET ranged from 3 percent to 8 percent (mean = 5.6 percent) of 100 percent DEET and 4 to 14 percent (mean = 8.4 percent) of the 15 percent DEET-in-ethanol formulation.

Table 5.5 compares dermal absorption in DEET reported in different studies and with different test subjects. However, these results may not accurately represent human exposure conditions, where individuals apply repeated doses of DEET to the skin without washing off previous doses.

Acute Effects

As with many pesticides, the majority of health effects reported to have been caused by DEET are acute. In fact, there appears to be no evidence in the literature that suggests chronic low-level exposure to DEET produces effects lasting months or years after exposure. DEET has been associated with a suite of symptoms, which are summarized in Table 5.6.

Federal law requires pesticides that were first registered before November 1, 1984, to be re-registered to ensure that they meet evolving, more stringent health standards. DEET was subjected to this process in 1998. The EPA concluded that DEET is generally of low acute toxicity, and on the basis of the available toxicological data, the agency stated that normal use of DEET does not present a health concern to the general U.S. population (USEPA, 1998a). It should be noted that the EPA assumes that the general population receives "subchronic exposure" to DEET; that is, users are expected to be exposed to DEET intermittently for only days or weeks.

Table 5.5

In Vivo and In Vitro Dermal Absorption of DEET

Reference	Species	Dose ($\mu g/cm^2$)	Solvent of Application	Collection Period (days)	Percent Absorbed
Feldman and Maibach, 1974	Human[a]	4	Acetone	5	16.17 ± 5.10
Moody and Nadeau, 1993)	Human[b]	44.7	Acetone	2	27.7 ± 4.24
Selim et al., 1995	Human[a]	625[c]	Technical-grade DEET	5	5.6 (range 3–8)
Selim et al., 1995	Human[a]	500[d]	Ethanol	5	8.4 (range 4–14)
Reifenrath et al., 1981	Hairless dog[a]	4	Ethanol	5	12.8 ± 4.6
Reifenrath et al., 1980	Hairless dog[a]	320	Ethanol	5	9.4 ± 3.6
Moody and Nadeau, 1993	Pig[b]	19.4	Acetone	2	15.3 ± 0.82
Reifenrath et al., 1984	Weanling pig[a]	4	Ethanol	5	9.4
Moody and Nadeau, 1993	Guinea pig[a]	12.5	Acetone	14	30.0 ± 5.96
Moody and Nadeau, 1993	Guinea pig[b]	12.5	Acetone	2	10.9 ± 1.40
Moody and Nadeau, 1993	Rat[a]	38.7	Acetone	14	41.0 ± 10.51
Moody and Nadeau, 1993	Rat[b]	38.7	Acetone	2	21.4 ± 2.17
Moody and Nadeau, 1993	Mouse[b]	33.3	Acetone	2	36.2 ± 27.5

Source: Stinecipher and Shah (1997), with additions and re-ordering in the present report.
[a]In vivo studies.
[b]In vitro studies.
[c]Approximation; the authors reported applying approximately 15 mg of 98.8 percent DEET to a 4 x 6-cm area.
[d]Approximation; authors reported applying approximately 12 mg of 15 percent DEET formulation in ethanol to a 4 x 6-cm area.

Table 5.6

Reported Signs and Symptoms of DEET Toxicity

Affected Area	Sign or Symptom
Cardiovascular	Hypotension
	Bradycardia
Dermatologic/allergic	Erythema
	Bullous eruptions
	Contact urticaria
	Anaphylaxis
Nervous system	Ataxia
	Confusion
	Slurred speech
	Muscle cramping
	Insomnia
	Tremor
	Clonic jerking
	Psychosis
	Seizures
	Coma

Source: Clem et al. (1993).

In studies using laboratory animals, DEET generally has been found to be of low acute toxicity. It is slightly toxic by the eye, dermal, and oral routes and has been placed in the EPA's Toxicity Category III (the second lowest of four categories) because of these effects (USEPA, 1998a).

Generally, neurotoxic symptoms dominate at near-lethal doses of DEET in rats and other animals. The rat oral LD_{50} is 2 to 4 g DEET/kg (Ambrose and Yost, 1965).[2] Rats given a single oral dose of 500 mg DEET/kg displayed increases in thermal response time and possible decreased rearing activity (Schoenig et al., 1993).

Most reports of severe DEET adversity in humans describe neurologic symptoms, and most of the severe adverse reactions occur in children (Veltri et al., 1994; Osimitz and Murphy, 1997; Fradin, 1998). Reports of DEET adversity have described manic psychosis, cardiovascular events, anaphylaxis, and several cases of contact urticaria and irritant contact dermatitis. These are included in Table 5.7, which summarizes reports of health effects on humans attributed to DEET exposure. It is possible that examples of DEET sensitivity may be missed, especially in children, as cases may easily be misdiagnosed as a viral encephalitis (Zadikoff, 1979). Deaths in adults have occurred following large doses, and blood levels of DEET in fatal systemic poisonings have ranged from 168 mg/L to 240 mg/L (Tenenbein, 1987). In contrast, a blood concentration of 3 mg/L was measured after routine application of a repellent to a 30-year-old male volunteer (Wu et al., 1979).

Manic psychosis occurred in a 30-year-old man who, for a period of three weeks, applied DEET daily and then sat in a light-bulb-heated box, apparently for self-medication to treat a rash. Sedation and incoherence were noted for short periods after each application session, and the man was admitted to a hospital after displaying aggressiveness and psychotic ideation. Clinical improvement (haloperidol) was complete within six days, atypical for classic endogenous mania. The authors point out the structural similarities between DEET and certain CNS-active drugs such as *N,N*-dimethyl acetamide and doxapram hydrochloride (Snyder et al., 1986).

A cardiovascular event occurred in a 61-year-old woman who applied a DEET-containing repellent (unknown concentration) "liberally" to all exposed skin prior to gardening. She suffered bradycardia and hypotension but recovered without sequelae (Clem et al., 1993). Other reports of cardiovascular DEET toxicity have included two cases of apparent suicide via ingestion of DEET-

[2] LD_{50} is the median lethal dose. This is a statistically derived single dose that can be expected to cause death in 50 percent of test animals when administered by the route indicated. It is expressed as the weight of a substance per unit weight of animal.

Table 5.7

Reported Health Effects in Humans Following the Topical Application of DEET

Reference	Affected Area	Sex/Age (yr); Possible Predisposition	DEET Concentration (%)	Pattern of Use (dermal unless otherwise noted)	Symptoms	Outcome
Heick et al., 1980	CNS	F/6; OCT heterozygote	15	≥10 occasions	Headaches, ataxia, disorientation, cerebral edema	Death
de Garbino and Laborde, 1983	CNS	F/1.5	20	Frequent	"Acute encephalopathy"	Death
Zadikoff, 1979	CNS	F/5	10	Nightly for 3 mo	Headaches, ataxia, seizures, agitation, opisthotonos, generalized edema	Death
Tenenbein, 1987	CNS	F/1	47.5	Ingested ≈25 mL	Seizures, opisthotonos	Recovery
Hall et al., 1975	CNS	F/7.5	10	Application and ingestion	Opisthotonos	Recovery
Zadikoff, 1979	CNS	F/1.5	10	Ingestion of unknown but probably small amount	Opisthotonos, ataxia	Recovery
Gryboski et al., 1961	CNS	F/3	15	Daily for 2 wk	Ataxia, encephalopathy	Recovery
Roland et al., 1985	CNS	F/8	15 & 100	Copious for 4 days	Seizures, rash, restlessness	Recovery
Edwards and Johnson, 1987	CNS	F/1.5	20	3 mo	Ataxia, movement disorder, drooling, opisthotonos, opsoclonus, myoclonus	Recovery
Lipscomb et al., 1992	CNS	M/5	100 & 15	Brief	Seizures	Recovery
MMWR, 1989	CNS	4 cases: M/3-7	NA	NA	Seizures	Recovery
Tenenbein, 1987	CNS	F/14	95	Ingested 50 mL	Unconsciousness, seizures	Recovery
MMWR, 1989	CNS	M/29	NA	NA	Seizures	Recovery
Veltri et al., 1994	CNS	M/17	17.9	Saturated clothing	Ataxia, possible seizure or unconsciousness	Recovery, incomplete follow-up
Veltri et al., 1994	CNS	M/adult; ingested phenothiazine drug same day	20.9	Sprayed entire body	Dystonia	Recovery

Table 5.7 (continued)

Reference	Affected Area	Sex/Age (y); Possible Predisposition	DEET Concentration (%)	Pattern of Use (Dermal Unless Otherwise Noted)	Symptoms	Outcome
Snyder et al., 1986	CNS	M/30	70	Daily application followed by dry sauna, 3 wk	Aggressiveness, psychotic ideation, psychomotor hyperactivity, rapid and pressured speech, tangentiality, flight of ideas, grandiose delusions, auditory hallucinations	Recovery
Veltri et al., 1994	Cardiovascular, CNS	M/33	NA	Intentionally ingested 8 oz of DEET repellent	Cardiorespiratory arrest, hyperglycemia (day 2), seizures, intravascular coagulopathy, cerebral edema	Death
Tenenbein, 1987	Cardiovascular, CNS (plus bowel)	F/33	95	Ingestion of up to 50 mL	Hypotension, seizure, coma, bowel infarction	Death
Veltri et al., 1994	Cardiovascular, CNS	M/33; self-reported diagnosis of Raynaud's Disease	NA (6-yr-old repellent product)	NA (potential inhalation during application 1 wk prior to symptoms)	Numbness, dizziness, vomiting, hypotension	Recovery, incomplete follow-up
Clem et al., 1993	Cardiovascular	F/61	NA	Liberal application, frequency NA	Bradycardia, hypotension	Recovery
Miller, 1982	Cutaneous or allergic reaction	F/42	52	Touched companion who had just applied repellent	Anaphylaxis	Recovery
Maibach and Johnson, 1975; von Mayenburg and Rakoski, 1994; Wantke et al., 1996	Cutaneous or allergic reaction	3 cases: 2 M + 1 F/4-35	NA	Urticaria developed 10-30 min after application	Wheals	Recovery
Reuveni and Yagupsky, 1982	Cutaneous or allergic reaction	10 cases: M/18-20	33-50	Military, applied to skin and then slept	Hemorrhagic bulla and erosions, confined to antecubital fossa	Recovery in 9 of 11; scarring in 2 of 11

Source: Adapted from Osimitz and Murphy (1997) and Fraden (1998).

CNS = central nervous system; NA = not available; OCT = ornithine carbamoyl transferase.

containing repellents (Tenenbein, 1987; Veltri et al., 1994). The case of anaphylaxis listed in Table 5.7 was a woman with brief exposure to DEET; her symptoms returned when she was re-exposed to DEET in an emergency room, indicating a possible hypersensitivity (Miller, 1982).

A particularly important study examined 9,086 human exposures to DEET-containing insect repellents that were reported to 71 Poison Control Centers (PCCs) between 1985 and 1989 (Veltri et al., 1994).[3] In these cases, most of the adverse effects were related to the route of exposure, rather than the age or gender of the patient or the concentration of DEET in the repellent formulation. Symptoms were most likely to occur following inhalation or ocular exposures, and these accounted for 2.0 percent and 31.9 percent of the total cases handled by the PCCs, respectively. Ingestion and multiple-route exposures accounted for 49.4 percent and 12.6 percent of all cases, respectively. Of all cases, 39.8 percent of the patients had symptoms that were considered related to DEET exposure; 54 percent of the patients were asymptomatic. After the study, 74.8 percent of the patients were followed long enough to determine a definitive outcome; of these, 98.9 percent either experienced no effects or had symptoms that were transient, resolved rapidly, and usually involved the skin or mucous membranes. Of 889 patients who were evaluated in a health care facility, 81.4 percent were discharged after initial treatment and 4.9 percent were admitted for medical care. (The remainder were lost to follow-up.) The authors suggest that in most patients, symptoms, if present, were not serious and resolved quickly. Sixty-six patients experienced more pronounced or prolonged symptoms, but these resolved without apparent sequelae. Five patients (all male) were reported to have suffered serious health effects. One had a dystonic reaction. He had ingested prochlorperazine (known to cause distonia) earlier in the day, so a synergistic reaction with DEET was not excluded. Two of the patients experienced eye irritation, which was treated at home. Two other patients were treated and released from an emergency room: A 17-year-old male who saturated his clothing with repellent (17.9 percent DEET) was ataxic and possibly suffered a seizure; a 33-year-old male experienced diminished sensation and hypotension one week after using repellent.

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[3]As the authors point out, the data analyzed were voluntarily reported to a national database by the PCCs. These data are useful but not without limitations: "The data included in this report were not obtained from a sample that is generalizable to the population of the US. The data represent those persons who have an exposure and report that exposure to a PCC. It is unknown how those persons differ from those who do not call a PCC." However, the cases reported do provide some insight into the common routes of exposure associated with specific health outcomes and some measure of the severity of effects.

Chronic, Reproductive, Genetic, and Carcinogenic Effects

As mentioned above, DEET underwent scrutiny during an EPA re-registration process in 1998 (USEPA, 1998a) which concluded that human exposure to DEET was usually brief, and long-term exposure was not to be expected. Based on laboratory animal studies, the EPA concluded that DEET is of low acute toxicity (Toxicity Category III). Further, DEET has been classified as an EPA Group D carcinogen (not classifiable as a human carcinogen), and mutagenicity tests for DEET (Ames assay, chromosomal aberration assay, and unscheduled DNA synthesis assay) were all negative, indicating that DEET is not mutagenic.

No reports were found of long-term effects in humans from chronic exposures to DEET (with the exception of rare reports of scarring), so there is no evidence to suggest such a scenario is of great concern in predicting the potential health effects of DEET in PGWV. As seen in Table 5.7, there have been some reports of subacute, subchronic, or possibly chronic human exposures to DEET; but with the exception of three deaths in children (at least one of whom was confirmed to have had a predisposing condition), these exposures resulted in no long-term effects. The following summarizes some of the animal studies considered by the EPA in the re-registration of DEET (USEPA, 1998a).

In a two-year chronic toxicity/carcinogenicity study in rats, 60 rats of each sex received 98.3 percent DEET in their diet. No toxicity was seen in male rats at the highest dose (100 mg/kg/day), but female rats displayed decreases in food consumption and body weight and an increase in cholesterol levels at their highest dose (400 mg/kg/day). At this same dietary concentration, 400 mg DEET/kg/day, beagle dogs in a separate one-year study displayed decreases in food consumption and body weight, an increase in the incidence of ptyalism, and a decrease in cholesterol levels. No compound-related effects on reproduction (e.g., fertility, gestation, or viability) were noted in rats given DEET in their diet at up to 5,000 ppm for two consecutive generations.

SYNTHESIS

Most reviews of DEET toxicity have concluded that the risk of adverse effects from DEET-containing repellents used as directed by the label appears low (Veltri et al., 1994; Osimitz and Grothaus, 1995; Fradin, 1998; Goodyer and Behrens, 1998). This conclusion is based on reviews of reported effects in humans, animal toxicology, and possible alternate etiologies for symptoms reported in most patients. In fact, hypersensitivity may be required for severe acute toxic effects to occur, and a suite of data from animal studies generated to support DEET registration provides no evidence of adverse long-term effects related to DEET exposure.

No correlation between the concentration of DEET in a repellent and the frequency or severity of effects is supported by the literature. Further, it is difficult to quantify consistently the temporal relationship between the onset of CNS symptoms and exposure to DEET, but the reaction is generally rapid, as is the resolution in most cases. There have been a relatively small number of severe adult effects related to DEET exposure. While a pattern of potentially severe neurotoxicity in children who have been exposed to DEET is emerging, the total number of reported cases is very small compared with the population exposed. This pattern has not been observed in adults. The reasons for this disparity are unknown but may be related to the fact that children have a different surface-area-to-volume ratio than adults. Generally, patients who are reported to present severe health effects related to DEET use recover without reported sequelae.

Concern about the interactive effect of DEET with other chemicals may be warranted (see Chapter Eight), but the available literature is not complete enough to allow definitive conclusions to be drawn at this point. It is difficult to extrapolate the results of animal studies to long-term human effects, and the possibility of chemical interactions compounds the uncertainty inherent in the process. This is not to say, however, that further research should not be undertaken. A prudent approach may be to, first, more accurately determine the exposures that warrant further study. If it is determined that coexposures warrant further investigation, it may be sensible to examine common routes of exposure for resulting bioavailability before investigating specific toxicological endpoints. In addition to this area for potential research, efforts to explain the broad variety of outcomes associated with DEET exposure may be warranted, especially for cases of hypersensitivity.

Chapter Six

PYRETHROIDS

The historical development of the synthetic pesticides called pyrethroids is based on the pyrethrins, which are derived from chrysanthemums. Pyrethrins are a "natural" environmental product that is of low toxicity to mammals. They are highly photolabile and degrade quickly in sunlight, and the cost of reapplying them has limited their widespread agricultural use. Pyrethroids have been synthesized to be similar to pyrethrins yet more stable in the environment. Evidence suggests that they have a very large margin of safety when used as directed by the label (Aldridge, 1990; Chen et al., 1991; Snodgrass, 1992).

Commercial pyrethroid products commonly use petroleum distillates as carriers. Some commercial products also contain OP or carbamate insecticides because the rapid paralytic effect of pyrethrins on insects ("quick knockdown") is not always lethal (Cheremisinoff and King, 1994). Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates for ULV application.

PERMETHRIN

General Information

Permethrin is a broad-spectrum pyrethroid insecticide. It is available in dusts, emulsifiable concentrates, smokes, ULV concentrates, and wettable-powder formulations. The chemical identity of permethrin is shown in Table 6.1, and Table 6.2 summarizes its physical and chemical properties.

Availability and Recommended Use of Permethrin During ODS/DS

Permethrin is part of the DoD Insect Repellent System[1] (Young and Evans, 1998) and was issued in the PGW as a ready-to-use insect repellent for clothing

[1]This system was known during the ODS/DS era as the DOD Repellent System. It later became known as the DOD Arthropod Repellent System and then the DOD Insect Repellent System. All

Table 6.1

Chemical Identity of Permethrin

Characteristic	Information
Chemical class	Pyrethroid
Chemical name	3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarbobylic acid (3-phenoxyphenyl)methyl ester
Trade names	Ambush, Ectiban, FMC 33297, NIA 33297, NRDC 143, Permethrin, Pounce, PP557, S3151, SBP 1513, PT Wasp Freeze & Hornet Killer, Wasp & Hornet Killer II, Wasp Stopper II Plus
Chemical formula	$C_{21}H_{20}Cl_2O_3$
CAS Registry number	52645-53-1

Table 6.2

Physical and Chemical Properties of Permethrin

Property	Information
Molecular weight	391.29
Color/form	Colorless crystals to a pale yellow viscous liquid
Odor	Odorless
Water solubility at 30°C	0.2 mg/mL
Partition coefficient (K_{ow})	3.0×10^3
Vapor pressure at 25°C	3.4×10^{-7} mm Hg
EPA toxicity classification	Class II or III, depending on formulation
ACGIH TLV–TWA	NA, Pyrethrum[a]: 5 mg/m^3
NIOSH REL–TWA	NA, Pyrethrum: 5 mg/m^3
NIOSH REL–STEL	NA
NIOSH IDLH value	NA, Pyrethrum: 5,000 mg/m^3
OSHA PEL–TWA	NA, Pyrethrum: 5 mg/m^3
EPA IRIS RfD	5×10^{-2} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA, Pyrethrum: A4
EPA	NA
IARC	NA

NA = not available.

[a]Because occupational health standards and recommendations are largely unavailable for permethrin and *d*-phenothrin, these values are provided for pyrethrum for comparison. Pyrethrum is a botanical insecticide, and its active components are the pyrethrins (cinerins I and II, jasmolin I and II, and pyrethrins I and II).

describe essentially the same system; Young and Evans (1998) provide a good description of this system. This system was also described in Technical Guide 174, *Personal Protective Techniques Against Insects and Other Arthropods of Military Significance*, U.S. Army Environmental Hygiene Agency, June 1991. The use of permethrin and DEET had been emphasized earlier during ODS/DS in an electronic message to the services and geographic Commanders in Chief (CINC) from the U.S. Armed Forces Pest Management Board ("Availability of permethrin aerosol for treatment of the Battle Dress Uniform (BDU)," NSN 6840-01-278-1336, dated August 1, 1990).

application (Table 6.3). It is labeled for use on clothes such as the battle dress uniform (BDU) and bed netting, to be applied as an aerosol spray six to eight inches away from the target surface for 30 seconds, every six weeks or after six launderings. Treated clothing should not be worn for two to four hours after application.

Permethrin Residues

Studies show that most of the airborne residues of permethrin, dispensed with different types of applicators, are settled within four hours of application (Lindquist, 1987). Studies on the residues remaining in apparel fabrics after laundering indicate that while fabric fiber content does not affect the removal of permethrin residues, fabric weight may contribute to post-laundering residue retention. Heavier fabrics were found to prevent pesticide penetration more than lighter fabrics, but heavier fabrics retain more residues after laundering. The type of detergent—heavy-duty liquid or phosphate powdered—did not affect the fraction of permethrin removed (Laughlin, 1991).

PHENOTHRIN

General Information

The compound *d*-phenothrin is labeled as an indoor-use aerosol insecticide, intended for purposes such as spraying bed netting (to kill insects trapped inside after installation) or spraying inside aircraft (to prevent transport of insects). The application rates are one 10-second spray per 1,000 ft^3 in aircraft and one 10-second spray per 1,000 ft^3 in buildings and tents; spraying should be done with a sweeping motion at least three feet away from surfaces. The indoor area should then stay closed for 30 minutes. Reapplication can be conducted as necessary. The chemical identity of *d*-phenothrin is shown in Table 6.4, and Table 6.5 summarizes its physical and chemical properties.

Table 6.3

Formulations of Permethrin Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-01-278-1336	Permethrin	Aerosol spray	0.5	6-oz can	Apply to battle dress uniforms, bed net, head net, and inside tent.

Table 6.4

Chemical Identity of *d*-Phenothrin

Characteristic	Information
Chemical class	Pyrethroid
Chemical name	2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester
Trade names	S-2539, Sumethrin, Sumitrin
Chemical formula	$C_{23}H_{26}O_3$
CAS Registry number	26002-80-2

Table 6.5

Physical and Chemical Properties of *d*-Phenothrin[2]

Property	Information
Molecular weight	350.46
Color/form	Pale yellow to yellow–brown liquid
Water solubility at 25°C	1.06 g/mL
Vapor pressure at 25°C	1.2×10^{-6} mm Hg
EPA toxicity classification	Class III
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	NA
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	NA
IARC	NA

NA = not available.

Availability and Recommended Use of *d*-Phenothrin During ODS/DS

During ODS/DS, *d*-phenothrin was available as a ready-to-use aerosol insecticide, to be used according to the label directions (Table 6.6).

Environmental Characteristics of *d*-Phenothrin

Studies have shown that *d*-phenothrin displays slight to no soil mobility (Swann et al., 1983) and volatilizes slowly from water (Meylan and Howard, 1991), although it may also adsorb to sediments (Meylan et al., 1992). It can exist in

[2]See Table 6.2 for comparable information on pyrethrum.

Table 6.6

Formulations of *d*-Phenothrin Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-01-067-6674	*d*-phenothrin	Aerosol spray	2	6 oz	Spray preformulated aerosol to buildings, vans, tents, and aircraft

the atmosphere in its vapor and particulate phases, with estimated half-lives of from approximately one-half to three hours (Howard, 1991).

d-Phenothrin Residues

A recent study designed to determine the behavior of *d*-phenothrin sprayed in a room under various conditions found that the air concentrations depended mainly on ventilation rates but not on circulation (Matoba, 1998). The applications were done using a commercial 300-mL aerosol canister containing 0.9 g of *d*-phenothrin. Spraying occurred during an eight-week period every two weeks for 2.5 minutes (considerably longer than the rate recommended on the label). The air concentrations peaked after each spraying to about 750 $\mu g/m^3$ and decreased rapidly (the half-life in air is 20 minutes) to an eight-week concentration of 2.35 $\mu g/m^3$ and an annual mean of 0.43 $\mu g/m^3$. There was little difference in air concentrations between samples collected at different room heights, and airborne *d*-phenothrin in the room did not accumulate with repeated sprays (Matoba, 1998).

POTENTIAL HEALTH EFFECTS OF PYRETHROIDS

Synthetic pyrethroids are among the newest pesticides to enter the marketplace, and they account for a large percentage of the pesticides in use today. Despite their extensive use, few poisonings in humans have been reported (Morgan, 1989). When acute pyrethroid intoxication occurs in rats, two patterns of symptoms are observed, depending on the chemical configuration of the modified pyrethrins. The type I pyrethroids, lacking a cyano group, produce the T syndrome (tremors, aggressive sparring, and enhanced startle response). The type II variants, containing a cyano group, produce the CS syndrome that includes choreoathetosis, salivation, and seizures. Both types interact with the sodium channel on neuronal cell membranes, delaying closure of these channels. Type II pyrethroids also block the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

This review focuses on permethrin and *d*-phenothrin, both of which are classified as type I pyrethroid insecticides.

Permethrin

Permethrin is a useful synthetic insecticide that has proven effective in a number of environmental and clinical settings. It appears to be more effective than DEET in protecting individuals from tick bites (either when sprayed or impregnated in battle uniforms) (Evans et al., 1990), but uniform impregnation alone was not found to be effective in preventing transmission of malaria in Thailand (Eamsila et al., 1994). In 1990, the U.S. military adopted permethrin as the standard clothing-application repellent, to be used as an adjunct to topical repellents (Young and Evans, 1998).

Permethrin exists in the *cis* and *trans* isomer forms. Studies demonstrate that the former is considerably more toxic to rats and mice than is the latter (Jaggers and Parkinson, 1979; Glickman et al., 1982). The majority of the literature regarding the health effects of permethrin consists of unpublished studies in the chemical and pesticide industries. These references are cited in the International Programme on Chemical Safety (IPCS), a joint effort undertaken by the United Nations, the International Labor Organization, and the World Health Organization (WHO, 1990). Discussions of the acute effects of permethrin exposure come from animal studies.

Acute Effects. The literature contains a limited number of references for permethrin, and those that are cited repeatedly describe the relative safety of this compound. A review of 573 cases of acute pyrethroid poisoning in the Chinese medical literature (He et al., 1989) focuses primarily on exposure to deltamethrin, fenvalerate, and cypermethrin, although it indicates that the spectrum of acute poisoning is similar for all pyrethroids. With occupational exposure, individuals experienced facial skin sensations (burning or itching), usually within a few hours of exposure. With ingestion, digestive symptoms included epigastric pain, nausea, and vomiting. Acute poisoning symptoms from all exposure routes are primarily related to the effects of pyrethroids on the nervous system and include dizziness, headache, nausea, anorexia, and fatigue. Muscle fasciculation and altered consciousness were reported in more severe cases with extensive exposures (He et al., 1989).

In a study using 10 volunteers (four men and six women), 30 percent of the subjects developed skin irritation after applying 1 percent permethrin to their skin (Farquhar et al., 1981b). Another study of dermal exposure showed minor skin irritation at approximately 30 minutes that peaked at eight hours and disappeared after one day (Flannigan and Tucker, 1985; Flannigan et al., 1985a,b). When their clothes were impregnated with 3.8 mg/day of permethrin, the vol-

unteers showed no signs of toxicity (Farquhar et al., 1981a). LeQuesne evaluated findings among 23 pest-control workers who were occupationally exposed to multiple compounds, including permethrin. Although the workers reported tingling, burning, and a rash starting 30 minutes after exposure and lasting up to eight hours, these findings were not exhibited among workers exposed to permethrin alone (LeQuesne et al., 1980).

After permethrin was introduced as an alternative treatment for head lice in humans, data were gathered regarding possible adverse effects from the use of a 1 percent permethrin creme rinse. Results on 18,950 individuals from 37 local public health departments showed few adverse reactions. The observed rate was approximately 2.2 adverse events per 1,000 administrations. Adverse events, although perhaps underreported in this post-marketing survey, were not clinically serious (Andrews et al., 1992). The most common adverse effects were itching and a rash. Other effects (e.g., shortness of breath, GI effects) occurred in only a few individuals.

Animal studies produce findings that support the effect of permethrin on the CNS. Poisoning was reported to start within two hours and to last up to three days following exposure. At very high levels, whole body tremors (mild to convulsive) occurred, sometimes with salivation. Additional evidence of poisoning included hyperactivity and hyperexcitability, urination, defecation, ataxia, and lacrimation (Parkinson, 1978; Litchfield, 1983). However, subjects in these studies were exposed to levels much higher than those that occur in occupational (pest-control operators), military (clothing impregnation), or clinical (treatment for lice) exposures. Acute effects of permethrin reported in three animal studies are shown in Table 6.7. Lethal exposure levels are given in Table 6.8.

The U.S. Army Environmental Hygiene Agency[3] evaluated the absorption of permethrin in individuals wearing permethrin-treated clothing (0.125 mg/cm^2) and found that the exposure dose is approximately 0.0006 mg/kg/day, orders of magnitude below levels that produced acute toxicity in animals (Snodgrass, 1992).

Chronic, Reproductive, Genetic, and Carcinogenic Effects. Data on chronic human exposure to permethrin come primarily from studies of pest-control workers and clinical evaluations of patients treated for scabies and lice infestations. Data again support the conclusion that permethrin is extremely safe when used in recommended applications (Table 6.9).

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[3]Subsequently renamed the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM).

Table 6.7

Acute Effects of Permethrin Reported in Animal Studies

Reference	Model	Concentration and Duration	Route	Effects
Okuno et al., 1976	Japanese white rabbits	0.5 mL technical grade to dorsal skin	Dermal	No irritation
Metker et al., 1977	Rabbits	0.05 mL 25% in ethanol	Dermal	No irritation
Okuno et al., 1976	Japanese white rabbits	0.1 mL technical grade washed at 5 min or 24 hr	Ocular	No irritation

Table 6.8

Lethal Exposure Levels of Permethrin Reported in Animal Studies

Reference	Model	Carrier	Route	LD_{50}
Parkinson et al., 1976	Female rabbit	None	Dermal	>2,000 mg/kg body weight
Parkinson et al., 1976	Female rats	None	Dermal	>4,000 mg/kg body weight
Parkinson, 1978	Male rats	Water	Dermal	>5,176 mg/kg body weight
Kohda et al., 1979	Mouse	None	Dermal	>2,500 mg/kg body weight
Clark, 1978	Rats	Xylene	Dermal	>750 mg/kg body weight
Kohda et al., 1979	Rats	None	Dermal	>2,500 mg/kg body weight
Sasinovich and Panshina, 1987	Rats	None	Dermal	2,000 mg/kg body weight
Parkinson et al., 1976	Rats	Water	Intraperitoneal	>3,200 mg/kg body weight
Parkinson et al., 1976	Female rabbit	Water	Oral	>4,000 mg/kg body weight
Parkinson et al., 1976	Female rats	Water	Oral	>4,000 mg/kg body weight
Piercy et al., 1976	Female Sprague Dawley rats	Corn oil	Oral	LD50 4,251 mg/kg body weight but 3,000 mg/kg for starved rats
Wallwork and Malone, 1974	Female Wistar rats	As is	Oral	>20,000 mg/kg body weight
		40% in corn oil		4,672 mg/kg body weight
		40% in petroleum distillate		>8,000 mg/kg body weight
		40% in DMSO		>8,000 mg/kg body weight
		20% in glycerol		>5,048 mg/kg body weight
Millner and Butterworth, 1977	Hen		Oral	>1,500 mg/kg body weight
Jaggers and Parkinson, 1979	Male rats	Corn oil	Oral	500 mg/kg body weight
Parkinson, 1978	Male rats	Water	Oral	2,949 mg/kg body weight
Clark, 1978	Mouse	DMSO	Oral	250–500 mg/kg body weight

Table 6.8 (continued)

Reference	Model	Carrier	Route	LD_{50}
Kohda et al., 1979	Mouse	Corn oil	Oral	Male: 650 mg/kg body weight Female: 540 mg/kg body weight
Parkinson et al., 1976	Mouse	Water	Oral	>4,000 mg/kg body weight
Braun and Killeen, 1975	Rats	Corn oil	Oral	1,200 mg/kg body weight
Clark, 1978	Rats	DMSO	Oral	Male: 1,500 mg/kg body weight Female: 1,000 mg/kg body weight
Kohda et al., 1979	Rats	Corn oil	Oral	Male: 430 mg/kg body weight Female: 470 mg/kg body weight
Sasinovich and Panshina, 1987	Rats	Water	Oral	1,725 mg/kg body weight
Kohda et al., 1979	Mouse	Corn oil	Subcutaneous	>10,000 mg/kg body weight
Kohda et al., 1979	Rats	Corn oil	Subcutaneous	Male: 7,800 mg/kg body weight Female: 6,600 mg/kg body weight

DMSO = dimethyl sulfoxide.

Table 6.9

Subacute and Chronic Effects of Permethrin in Humans

Reference	Subjects	How Applied/Exposed	Absorption	Manifestations and Effects
Kolmodin-Hedman et al., 1982	6 forestry workers	2% aqueous emulsion, inhalation by occupational exposures	1 had detectable levels early	None.
Pegum and Doughty, 1978	17 volunteers	1% in soft paraffin, up to 9 days		2 of 17 developed mild erythema.
Wieseler et al., 1998	22 pest-control operators, 3 specifically exposed to permethrin	Normal commercial application of pyrethroid mix containing permethrin, 1-21 yr		No blood, heart, lung, liver, or nervous system abnormalities. No correlation between the number of complaints and pyrethroid metabolite concentration in urine. Only fatigue was more common in the pyrethroid exposed group. No specific pyrethroids were discussed.

Animal studies of subacute and chronic exposure, even at high doses, generally fail to show any lasting effects (Table 6.10). Only at extremely high doses do animals begin to demonstrate evidence of neurologic impairment. Animal studies repeatedly conclude that the potential for permethrin to induce cancer, even at fairly high exposures, is weak at best (WHO, 1990). In vitro and in vivo tests fail to reveal a mutagenic potential for permethrin (Anderson and Richardson, 1976; Longstaff, 1976; McGregor and Wickramaratne, 1976; Miyamoto, 1976; Newell and Skinner, 1976; Simmon, 1976; Clive, 1977; Suzuki, 1977; Woodruff et al., 1983; Pluijmen et al., 1984; Surralles et al., 1995). Mouse studies with permethrin doses of up to 150 mg/kg body weight from day seven to day 12 of pregnancy failed to show any effect on the pregnant females or offspring (Kohda et al., 1976). Sprague Dawley rat findings were similar with doses of up to 50 mg/kg body weight from day nine to day 14 of pregnancy (Kohda et al., 1976).

Others reported similar findings when exposing CD rats (doses of up to 225 mg/kg, day six to day 16) (McGregor and Wickramaratne, 1976), Sprague Dawley rats (doses of up to 83 mg/kg diet, day six to day 16) (Metker et al., 1977), and Wistar rats (doses of up to 200 mg/kg body weight, day six to day 16) (James, 1974) to permethrin. Dutch rabbits were exposed to 600, 1,200, or 1,800 mg/kg body weight per day (Richards et al., 1980). At all levels, body weight gain decreased, and the two highest doses were embryotoxic but not teratogenic.

Reproductive studies also fail to show any attributable adverse effects from fairly high doses of permethrin: in Long-Evans rats (up to 100 mg/kg in the diet for three generations) (Schroeder and Rinehart, 1977); in Wistar rats (up to 2,500 mg/kg in the diet for 12 weeks [Hodge et al., 1977] or up to 180 mg/kg body weight for three generations [James, 1979]); and in Sprague Dawley rats (up to 4,000 mg/kg in the diet, day six to day 15 of pregnancy) (Spencer and Berhance, 1982).

d-Phenothrin

The literature cites very few references for *d*-phenothrin, and those that are cited repeatedly address the relative safety of this insecticide, and of the pyrethroids in general. The majority of the literature consists of unpublished studies from the chemical and pesticide industry. These references are cited in the International Programme on Chemical Safety (IPCS), a joint effort undertaken by the United Nations, the International Labor Organization, and the World Health Organization (IPCS, 1990).

Acute Effects. The acute effects of *d*-phenothrin on animals are summarized in Table 6.11. The studies cited show toxicity but only at extremely high doses and in routes inconsistent with conventional exposure in humans. Suzuki et al. (1981) failed to show genetic effects on bone marrow with high intraperitoneal doses at up to two days following exposure.

Table 6.10

Subacute and Chronic Effects of Permethrin in Animals

Reference	Model	Concentration and Duration	Exposure Route	Effects
Franz et al., 1996	Hartley male guinea pigs	2 mL 5% permethrin cream for 3 days to a 6 x 8 cm shaved skin	Dermal	Systemic exposure following dermal application was found to be 40 to 400 times lower for 5% permethrin than for 1% lindane.
Flannigan et al., 1985b	New Zealand white rabbits	0.13 mg/cm^2 for 16 days	Dermal	Slight erythema.
Metker et al., 1977	New Zealand white rabbits	0.10, 0.32, 1.0 g/kg body weight for 21 days	Dermal	No effect.
Metker et al., 1977	New Zealand white rabbits	1.25 or 0.125 mg/cm^2 to skin on cloth twice weekly for 3 wk	Dermal	No effect.
Metker, 1978	Beagle dogs	125, 250, or 500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Male Hartley guinea pigs	125, 250, or 500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Sprague Dawley rats	125 or 250 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Sprague Dawley rats	500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	Shortened hexobarbital-induced sleeping time; tremors for first week.
Chesher and Malone, 1974b	New Zealand white rabbits	40% in corn oil 0.1 mL	Ocular	No effect.
Clapp et al., 1977b	Alderly Park mice	200, 400, 2,000, or 4,000 mg/kg diet for 28 days	Oral	No effect on mortality, growth, food utilization.
Clapp et al., 1977b	Alderly Park mice	80 mg/kg diet for 2 weeks, then 10,000 mg/kg for 2 wk	Oral	Weight loss and poor food utilization at 10,000 mg/kg start.
Chesher et al., 1975	Beagle dogs	500 mg/kg body weight for 14 days	Oral	No observed effect.
Killeen and Rapp, 1976a	Beagle dogs	5, 50 mg/kg body weight in gelatin capsules for 3 mo	Oral	No effect except increased liver weight at 50 mg/kg.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Killeen and Rapp, 1976a	Beagle dogs	500 mg/kg body weight in gelatin capsules for 3 mo	Oral	Clinical evidence of poisoning. Normal growth, food consumption, and laboratory parameters.
Reynolds et al., 1978	Beagle dogs	Up to 250 mg/kg body weight for 6 mo	Oral	No observed effect.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	20 mg/kg diet for 2 yr	Oral	No effect.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	500 mg/kg diet to wk 19, 5,000 mg/kg next 2 wk, 500 mg/kg rest of 2 yr	Oral	Increased liver weight. No neoplastic effect or laboratory parameter abnormalities.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	100 mg/kg diet to wk 21, 4,000 mg/kg diet thereafter	Oral	Decreased glucose but no other laboratory finding. No oncogenic effects.
Butterworth and Hend, 1976	Charles River (CD) rats	30, 100, 300 mg/kg diet for 5 wk	Oral	No effect.
Butterworth and Hend, 1976	Charles River (CD) rats	1,000 mg/kg diet for 5 wk	Oral	Increased liver weight in males.
Butterworth and Hend, 1976	Charles River (CD) rats	3,000 mg/kg diet for 5 wk	Oral	Increased liver weight in females. In all: persistent tremors, growth inhibition. No mortality. Slight increase in prothrombin time.
Hend and Butterworth, 1977	Charles River rats	6,000 mg/kg diet up to 14 days	Oral	11 of 12 died. Histologically there were frequent fragmented, swollen sciatic nerve axons and myelin degeneration.
Clapp et al., 1977b	Female Alderly Park mice	At least 2,000 mg/kg diet	Oral	Increased liver, kidney, heart, and spleen weight.
Chesher and Malone, 1974a	Female Dutch rabbits	200, 400, 800 mg/kg body weight	Oral	No significant laboratory abnormalities although more marked weight loss at the 800 mg/kg dose.
Wallwork et al., 1974	Female mice	200, 400, 800, 1,600 mg/kg body weight for 10 days in corn oil	Oral	Spasm and convulsion only in 1,600 mg/kg dose with 50% mortality. No hematology, chemistry, or body weight differences.
Millner and Butterworth, 1977	Hens	1 g/kg 40% solution in DMSO for 5 days	Oral	No delayed neurotoxic effect at 3 wk following exposure.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Ross and Prentice, 1977	Hens	9 g/kg body weight day 1 and 9	Oral	No neurologic signs or histopathologic changes in nervous system at 21 days after the last dose.
Edwards and Iswaran, 1977	Lactating cows	0, 0.2, 1.0, 10, or 50 mg/kg diet for 28 days	Oral	No effect.
Killeen and Rapp, 1976b	Long-Evans rats	0, 20, 100, 500 mg/kg diet for 90 days	Oral	No abnormal laboratory results or mortality. Tremors mostly during first week with 500 mg/kg dose. 100 and 500 mg/kg doses showed increased liver weight.
Braun and Rinehart, 1977; Billups, 1978a; Billups, 1978b	Long-Evans rats	0, 20, 100, 500 mg/kg diet for 2 yr	Oral	No oncogenic potential, no mortality, growth, or food consumption effect. No ophthalmology or laboratory effects except increased glucose at 18 months in females and 24 months in males.
Dyck et al., 1984	Long-Evans rats	Up to 500 mg/kg diet for 2 yr and up to 100 mg/kg diet for 3 generations	Oral	No nerve morphological changes related to feeding of permethrin.
Metker et al., 1977	Long-Evans rats	27, 54, 108 mg/kg body weight for 14 days	Oral	No effect.
Metker et al., 1977	Long-Evans rats	216 and 432 mg/kg body weight for 14 days	Oral	Muscle tremors.
Metker et al., 1977	Long-Evans rats	432 mg/kg body weight for 14 days	Oral	50% of females died.
Clapp et al., 1977b	Male Alderly Park mice	At least 10,000 mg/kg diet	Oral	Increased liver, kidney, heart, and spleen weight.
Glaister et al., 1977	Male Wistar rats	2,500, 3,000, 3,750, 4,500, 5,000, and 7,000 mg/kg diet for 14 days	Oral	Poisoning and death at two highest doses. At lowest doses, signs and symptoms disappeared after a week. Ultrastructural changes were present at the highest 2 doses, including vacuolation and swelling of unmyelinated fibers and Schwann cell hypertrophy.
Ishmael and Litchfield, 1988	SPF Alderly Park strain mice	250 mg/kg diet for 2 yr	Oral	No effect.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Ishmael and Litchfield, 1988	SPF Alderly Park strain mice	1,000, 2,500 mg/kg diet for 2 yr	Oral	No mortality effect. No carcinogenic effect. Liver showed proliferation of smooth endoplasmic reticulum on ultrastructural examination.
Kadota et al., 1975	Sprague Dawley rats	0, 375, 750, 1,500 mg/kg diet for 6 mo	Oral	No effect.
Kadota et al., 1975	Sprague Dawley rats	3,000 mg/kg diet for 6 mo	Oral	No clinical laboratory abnormalities. Hyperexcitability and tremors occurred.
Metker et al., 1977	Sprague Dawley rats	54, 108, 216 mg/kg body weight for 14 days	Oral	No effect.
Metker et al., 1977	Sprague Dawley rats	432, 864, or 1,728 mg/kg body weight for 14 days	Oral	Muscle tremors.
Metker et al., 1977	Sprague Dawley rats	1,728 mg/kg body weight for 14 days	Oral	23 of 24 died.
Dayan, 1980	Sprague Dawley rats	Up to 9,000 mg/kg diet for 21 days	Oral	Severe trembling and weight loss. However, evaluation of brain, spinal cord, trigeminal and dorsal root ganglia, proximal and distal root trunks, and terminal motor and sensory nerves did not demonstrate consistent histopathology.
Clapp et al., 1977a	Wistar rats	0, 200, 500 mg/kg diet for 4 wk	Oral	No effect.
Clapp et al., 1977a	Wistar rats	1,000 mg/kg diet for 4 wk	Oral	Nonspecific signs of poisoning.
Clapp et al., 1977a	Wistar rats	2,500 mg/kg diet for 4 wk	Oral	Hyperexcitability and increased liver weight.
Clapp et al., 1977a	Wistar rats	5,000 mg/kg diet for 4 wk	Oral	Decreased food consumption. No significant change in lab parameters.
Clapp et al., 1977a	Wistar rats	10,000 mg/kg diet	Oral	All died within 3 days.
Ishmael and Litchfield, 1988	Wistar rats	500, 1,000 mg/kg diet for 2 yr	Oral	Increased liver and kidney weight at both levels; increased smooth endoplasmic reticulum at 1 yr but not at 2 yr.
Ishmael and Litchfield, 1988	Wistar rats	2,500 mg/kg diet for 2 yr	Oral	Tremors and hyperexcitability for 2 wk. No related mortality; no change in growth or food consumption. No laboratory abnormalities. Increased smooth endoplasmic reticulum.

Table 6.11

Acute Effects of *d*-Phenothrin in Animals

Reference	Model	Concentration/ Duration	Route of Exposure	Manifestations and Effects
Segawa, 1979b	Sprague Dawley rats	>10,000 mg/kg body weight	Oral, subcutaneous, dermal, intraperitoneal	LD_{50}.
Segawa, 1979a	DdY mice	>10,000 mg/kg body weight	Oral, subcutaneous, intraperitoneal	LD_{50}.
Segawa, 1979a	DdY mice	>5,000 mg/kg body weight	Dermal	LD_{50}.
Kohda et al., 1979	Sprague Dawley rats	>3,760 mg/m^3	Inhalation	4-hr LC_{50}; no neurotoxicity observed.
Kohda et al., 1979	ICR mice	>1,180 mg/ m^3	Inhalation	4-hr LC_{50}.
Hiromori et al., 1984	ICR mice	265-315 mg/kg	Intravenous	LD_{50}.
Okuno et al., 1978	Sprague Dawley rats	5,000 mg/kg body weight per day for 5 days	Oral	1 of 10 females died after 4 doses. Signs of toxicity (piloerection, urinary incontinence) appeared but rapidly resolved after discontinuation.
Suzuki et al., 1981	ICR mice	2,500, 5,000, or 10,000 mg/kg once, then bone marrow examined at 6, 24, and 48 hr	Intraperitoneal	No chromosomal aberrations.

The literature does not provide evidence of *d*-phenothrin toxicity to humans. Hashimoto et al. (1980) found no adverse effects (dermal irritation, clinical signs, blood chemistry, or hematology) following dermal exposure of volunteers at concentrations of 0.44 to 0.67 mg/kg body weight per day for three days. Matoba modeled the risk assessment following residual spraying of *d*-phenothrin; and with aerosolization of 0.9 g *d*-phenothrin (and 1.1 g d-tetramethrin) in a 300 mL container, there was a 24,400 margin of safety (21,300 for infants) even under the worst conditions (windows closed, contrary to label instructions) (Matoba et al., 1998). The margin of safety is defined as the NOEL/exposure; the study used animal data to estimate the NOEL.[4]

[4]The no observable effect level (NOEL) is the lowest administered dose or exposure that results in no statistically significant difference from control.

Table 6.12

Chronic Effects of *d*-Phenothrin in Animals

References	Model	Concentration/ Duration	Route of Exposure	Manifestations and Effects
Murakami et al., 1981	Sprague Dawley rats	Up to 10,000 mg/kg per day for 6 mo	Oral	No effect on mortality, clinical signs, ophthalmology, urinalysis, or histopathology. NOEL M:F reported to be 55.4:63.3 mg/kg/day.
Martin et al., 1987	Fisher-344 rats	Up to 3,000 mg/kg per day for 105-118 days	Oral	No clinical signs, mortality, or food and water consumption, ophthalmology, blood biochemistry, urinalysis, or hematology changes. No oncogenic activity. NOEL M:F reported to be 47:56 mg/kg/day.
Amyes et al., 1987	B6C3F$_1$ hybrid mice	Up to 3,000 mg/kg per day for 2 yr	Oral	No clinical signs, mortality, ophthalmology, blood, urinalysis, or hematology changes. No tumor profile changes. NOEL M:F reported to be 40:164 mg/kg/day.
Pence et al., 1981	Beagle dogs	Up to 1,000 mg/kg in diet for 26 wk	Oral	No effects on mortality, clinical signs, body weight, food consumption, ophthalmology, histopathology, hematology, or urinalysis. NOEL reported to be 300 mg/kg diet per day.
Cox et al., 1987	Beagle dogs	Up to 1,000 mg/kg in diet per day for 1 yr	Oral	No effects on clinical signs, body weight, food consumption, ophthalmology, or urinalysis. NOEL M:F reported to be 8.24:26.77 mg/kg body weight/day.
Cox et al., 1987	Beagle dogs	3,000 mg/kg in diet per day for 1 yr	Oral	Decreased erythrocyte count, hemoglobin, and hematocrit, decreased total protein, increased liver weight, histopathological changes in adrenal and liver in some animals.
Rutter, 1974	New Zealand white rabbits	0, 10, 100, or 1,000 mg/kg body weight days 6-18 of gestation, sacrificed at day 29 or 30	Oral	No abnormalities in the does or fetuses (implantation sites, corpora lutea, resorption sites, weight, condition, viability). No effects on gestation.
Nakamoto et al., 1973	ICR mice	0, 30, 300, 3,000 mg/kg body weight days 7–12 of gestation, sacrificed on day 18 of gestation	Oral	No adverse effects as indicated by maternal growth, fetal mortality, and external and internal examination of fetuses for teratogenic or embryotoxic effects.
Nakamoto et al., 1973	ICR mice	0, 300, 3,000 mg/kg body weight days 7-12 of gestation, pups examined 29 days after delivery	Oral	No adverse effects as indicated by maternal growth, fetal mortality, and external and internal examination of fetuses for teratogenic or embryotoxic effects.
Tesh et al., 1987	Charles River CD rats	Up to 1,000 mg/kg diet for 3 generations	Oral	No effect on mortality, somatic growth, development, or reproductive performance. NOEL stated to be 1,000 mg/kg diet.
Tesh et al., 1987	Charles River CD rats	3,000 mg/kg diet for 3 generations	Oral	No effect on mortality, body weight, reproductive performance. Third generation normal. Slight increase in liver weight for first two generations.

Chronic, Reproductive, Genetic, and Carcinogenic Effects. The chronic effects of *d*-phenothrin on animals are summarized in Table 6.12. The studies cited show toxicity but only at extremely high oral doses that are inconsistent with conventional human exposure. Even at these high exposures, reproductive, genetic, and carcinogenic effects were not observed.

The literature does not provide evidence of chronic *d*-phenothrin toxicity to humans.

SYNTHESIS

Pyrethroids, particularly permethrin and *d*-phenothrin, are safe and effective when used in recommended applications. Studies show that these compounds are potentially toxic at extremely high exposures; however, when used in conventional ways, only minor skin irritation in sensitive individuals results. Clinical manifestations subside after short periods when the inciting exposure is discontinued.

Chapter Seven

ORGANOPHOSPHATES AND CARBAMATES

ORGANOPHOSPHATES

Organophosphate (OP) compounds were first synthesized in significant quantities during the 1940s, when tetraethylpyrophosphate was developed as an insecticide.

Azamethiphos

General Information. Azamethiphos is an OP pesticide that was probably procured locally during the PGW as a fly bait. While there is no EPA registration number for azamethiphos, it has been used in Canada, Scandinavia, the United Kingdom, and France to control sea lice infestations in fish farms. Azamethiphos is also available in Mexico, primarily for fly control. Commercially available azamethiphos products outside the United States include Alfacron 10 and Snip.

Alfacron 10 contains 10 percent azamethiphos as the active ingredient and is used as a wettable powder. A thick paste is obtained by mixing 200 mL of tepid water with 250 g of Alfacron 10, which will cover either 100 m^2 of floor space or 200 m^2 of walls. Alfacron can also be applied by spraying or painting with a liquid solution of 500 g Alfacron 10 in 4 L of tepid water. This mixture will cover 50 m^2 of floor space or 100 m^2 of wall surfaces. Snip is a 1 percent azamethiphos fly bait that contains Z-9 tricosene (female housefly pheromone), which attracts flies to eat the granular bait. The recommended application is 200 g of Snip spread on a 100 m^2 space frequented by flies. The bait becomes more effective if the space has been previously wetted with water or milk.

The chemical identity of azamethiphos is shown in Table 7.1, and Table 7.2 summarizes its physical and chemical properties.

Table 7.1

Chemical Identity of Azamethiphos

Characteristic	Information
Chemical class	Organophosphate
Chemical name	Phosphorothioic acid, S-{[6chloro-2-oxooxazolo(4,5*b*)pyridin-3-(2*H*)-yl]methyl} *O,O*-dimethyl ester
Trade names	Alfacron 10; Snip Fly Bait
Chemical formula	$C_9H_{10}ClN_2O_5PS$
CAS Registry number	35575-96-3

Table 7.2

Physical and Chemical Properties of Azamethiphos

Property	Information
Molecular weight	324.68
Color/form	Orange yellow granules or gray to white crystalline powder
Water solubility at 20°C	0.11 mg/mL (soluble in organic solvents such as methylene chloride, benzene, methanol, hexane, and n-octanol)
EPA toxicity classification	Class III
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	NA
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	NA
IARC	NA

NA = not available.

Availability and Recommended Use of Azamethiphos During ODS/DS. Both Alfacron 10, a wettable powder, and Snip, a granular bait, were reported to have been used during the PGW, and both were probably obtained locally (OSAGWI, personal communication). No NSN exists for azamethiphos-containing products.

Chlorpyrifos

General Information. Chlorpyrifos is a broad-spectrum insecticide originally used primarily to kill mosquitoes, although it is no longer registered for this use. It is registered for a variety of uses and sites and is effective in controlling cutworms, corn root worms, cockroaches, grubs, flies, termites, fire ants, and lice.

Chlorpyrifos acts primarily as a contact poison, with some action as a systemic poison. It is available in a variety of formulations, including granules, wettable powder, dustable powder, and emulsifiable concentrate.

The chemical identity of chlorpyrifos is shown in Table 7.3, and Table 7.4 summarizes its physical and chemical properties.

Availability and Recommended Use of Chlorpyrifos During ODS/DS. The chlorpyrifos products shipped to the Persian Gulf during ODS/DS are shown in Table 7.5.

Table 7.3

Chemical Identity of Chlorpyrifos

Characteristic	Information
Chemical class	Organophosphate
Chemical name	*O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate
Trade names	Brodan, Detmol UA, DMS-0971, Dowco 179, Dursban, Empire, ENT-27, 311, Eradex, Lorsban, Pageant, Piridane, Pyrinex, Scout, Stipend
Chemical formula	$C_9H_{11}Cl_3NO_3PS$
CAS Registry number	2921-88-2

Table 7.4

Physical and Chemical Properties of Chlorpyrifos

Property	Information
Molecular weight	350.62
Color/form	White to tan crystalline solid with amber oil
Odor	Mild sulfur/mercaptan
Water solubility at 25°C	2 mg/L
Partition coefficient (K_{ow})	9.1×10^4
Soil sorption coefficient (K_{oc})	6,070
Vapor pressure at 20°C	1.87×10^{-5} mm Hg
EPA toxicity classification	Class II
ACGIH TLV–TWA	0.2 mg/m^3 (skin)
NIOSH REL–TWA	0.2 mg/m^3 (skin)
NIOSH REL–STEL	0.6 mg/m^3 (skin)
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	3×10^{-3} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A4
EPA	NA
IARC	NA

NA = not available.

Table 7.5

Formulations of Chlorpyrifos Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Method
6840-00-402-5411	Dursban 4E	Liquid	40.8–42.8	5-gal can	Hand spray gun
6840-01-203-6161	Dursban 1.5 ULV	Liquid	19.36	5-gal can	Hand spray gun
6840-01-210-3392	Dursban L.O.	Liquid	42	40-mL bottle	Hand spray gun

Source: Provided by OSAGWI.

Environmental Characteristics of Chlorpyrifos. Due to its strong affinity for organic soils, chlorpyrifos adsorbs strongly to soils and sediments, and leaching and runoff are not significant. Adsorbed chlorpyrifos degrades under UV light, via chemical hydrolysis, and by the action of soil microbes. The soil half-life of chlorpyrifos ranges from two weeks to more than one year, depending on soil texture, soil pH, and climate. When applied to moist soils, chlorpyrifos has a volatility half-life of 45 to 163 hours, with 62 to 89 percent of the application remaining on the soil after 36 hours (Kamrin, 1997).

Chlorpyrifos Residues. Perhaps most important for estimating human exposures are studies of the fate of chlorpyrifos following its application. In one representative study of chlorpyrifos residues following application for residential termite control, ambient air samples and floor wipe samples were taken for seven days after either broadcast or total-release aerosol applications (Lu, 1998). The ambient air samples were taken at a height of one meter. The entire study was conducted with no ventilation and again when the area was ventilated with forced air for 30 minutes immediately after application. The results are summarized in Table 7.6. Peak air concentrations of 0.118 mg/m^3 (broad-

Table 7.6

Air and Surface Chlorpyrifos Residues Following Residential Broadcast and Aerosol Applications

	Chlorpyrifos Deposited							
	Broadcast Application				Aerosol Application			
	Vent On		Vent Off		Vent On		Vent Off	
Days After Application	Air (mg/m^3)	Wipe ($\mu g/cm^2$)	Air (mg/m^3)	Wipe ($\mu g/cm^2$)	Air (mg/m^3)	Wipe ($\mu g/cm^2$)	Air (mg/m^3)	Wipe ($\mu g/cm^2$)
1	0.0405	0.122	0.0424	0.105	0.0197	0.061	0.0457	0.063
2	0.0155	0.024	0.0180	0.019	0.0082	0.015	0.0102	0.010
3	0.0032	0.008	0.0046	0.020	0.0061	0.002	0.0084	0.002
4	0.0079	0.005	0.0082	0.003	0.0016	0.003	0.0063	0.001
5	0.0040	0.004	0.0011	0.004	0.0002	0.003	0.0006	0.003
6	0.0024	0.002	0.0010	0.003	0.0026	0.002	0.0004	0.002
7	0.0011	0.006	0.0023	0.006	0.0005	0.001	0.0023	0.002

Source: Compiled from Lu (1998).

cast) and 0.082 mg/m^3 (aerosol) were measured four hours after application. More chlorpyrifos was deposited on the carpet floors by broadcast applications than by aerosol applications. Residues on non-target surfaces (e.g., furniture) were greater with aerosol applications than with broadcast applications. Similar decay rates were observed in other studies (Gurunathan, 1998), and similar residue fractions were measured in studies conducted in homes and offices (Fenske, 1990; Currie, 1990).

Diazinon

General Information. Diazinon is an insecticide used to control cockroaches, silverfish, ants, and fleas in residential, non–food-preparation buildings. It is used as a bait to control scavenger yellow jackets in the western United States. Diazinon is also commonly used in home gardens and on farms to control a wide variety of sucking and leaf-eating insects. It is available in dust, granules, seed dressings, wettable powder, and emulsifiable solution formulations.

The chemical identity of diazinon is shown in Table 7.7, and Table 7.8 summarizes its physical and chemical properties.

Availability and Recommended Use of Diazinon During ODS/DS. The diazinon formulations that were shipped to the Persian Gulf during ODS/DS are listed in Table 7.9.

Environmental Characteristics of Diazinon. Diazinon has low persistence in soil, with a half-life of two to four weeks. It seldom migrates below the top half-inch of soil, but in some instances it may contaminate groundwater. The breakdown in water depends on acidity: At high acidic levels, diazinon has a half-life of 12 hours, while in neutral solution the half-life can reach six months (Kamrin, 1997).

Diazinon Residues. Airborne and surface concentrations of diazinon were measured after broadcast spray application on the floors of offices. A 1 percent solution of diazinon in water was applied at approximately 0.03 L/m^2 of floor

Table 7.7

Chemical Identity of Diazinon

Characteristic	Information
Chemical class	Organophosphate
Chemical name	O,O-diethyl 0-[6-methyl-2-(1-methylethyl-4-pyrimidinyl) ester
Trade names	G-24480, Antigal, Basudin, Diazol, D-z-n, Garden Tox, HelfaCat, HelfaDog, Neocidol, Parasitex, Sarolex, Spectracide, Taberdog, Tabercat
Chemical formula	$C_{12}H_{21}N_2O_3PS$
CAS Registry number	333-41-5

Table 7.8

Physical and Chemical Properties of Diazinon

Property	Information
Molecular weight	304.36
Color	Colorless (technical grade); pale yellow to dark brown
Odor	Faint ester-like odor
Water solubility at 25°C	40 mg/L
Soil sorption coefficient (K_{oc})	$6.45 \times 10^{+3}$
Vapor pressure at 20°C	1.4×10^{-4} mm Hg
EPA toxicity classification	Class II
ACGIH TLV–TWA	0.1 mg/m^3 (skin)
NIOSH REL–TWA	0.1 mg/m^3 (skin)
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	9×10^{-5} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A4
EPA	NA
IARC	NA

NA = not available.

Table 7.9

Formulations of Diazinon Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-00-753-5038	Diazinon Dust	Powder	2	25-lb	Dust as provided
6840-00-782-3925	Diazinon 4E	Liquid	48EC	Pail	Prepare solution

surface. The airborne diazinon concentration peaked four hours after application, at 0.16 mg/m^3, and it remained at nearly the threshold limit value 24 hours after application when rooms were unvented. Surface concentrations of diazinon were highest at 48 hours after application, 38 ng/cm^2 (Currie, 1990).

Dichlorvos

General Information. Dichlorvos is used to control household and stored-product insects. It is effective against flies, aphids, spiders, and caterpillars, acting as both a contact and a stomach poison. Dichlorvos is also used as a fumigant and has been used to make pet collars and pest strips.

The chemical identity of dichlorvos is shown in Table 7.10, and Table 7.11 summarizes its physical and chemical properties.

Table 7.10

Chemical Identity of Dichlorvos

Characteristic	Information
Chemical class	Organophosphate
Chemical name	2,2-dichlorovinyl dimethyl phosphate
Trade names	SD 1750, Astrobot, Atgard, Canogard, DDVP, Dedevap, Dichlorman, Divipan, Equigard, Equigel, Estrosol, Herkol, No-Pest Strip, Nogos, Nuvan, Task, Vapona, Vaportape II, Verdisol
Chemical formula	$C_4H_7Cl_2O_4P$
CAS Registry number	62-73-7

Table 7.11

Physical and Chemical Properties of Dichlorvos

Property	Information
Molecular weight	220.98
Color	Colorless to amber oily liquid
Odor	Mild chemical odor; aromatic odor
Water solubility at 20°C	10 mg/mL
Partition coefficient (K_{ow})	5.0×10^{-3}
Soil sorption coefficient (K_{oc})	14.5
Vapor pressure at 25°C	1.2×10^{-2} mm Hg
EPA toxicity classification	Class I
ACGIH TLV–TWA	0.9 mg/m^3 (skin)
NIOSH REL–TWA	1 mg/m^3 (skin)
NIOSH REL–STEL	NA
NIOSH IDLH value	100 mg/m^3
OSHA PEL–TWA	1 mg/m^3 (skin)
EPA IRIS RfD	5×10^{-4} mg/kg/day
EPA IRIS RfC	5×10^{-4} mg/m^3
Carcinogenicity classification	
ACGIH	A4
EPA	B2
IARC	2B

NA = not available.

Availability and Recommended Use of Dichlorvos During ODS/DS. Dichlorvos was available during ODS/DS in the commercial product No-Pest Strip (Table 7.12).

Dichlorvos Residues. Few studies of dichlorvos residues from pest strips have been conducted in the past 25 years. However, trials have been carried out to determine the concentrations of dichlorvos that occur in the air of houses when strips are placed under conditions of normal domestic use. Ten trials were conducted in Australia and France between 1967 and 1970. Two trials were also carried out in the United Kingdom. Samples of air were taken at regular inter-

Table 7.12

Formulations of Dichlorvos Available During ODS/DS

NSN	Name	Form	Formulation (% by wt)	Unit Size	Application Directions
6840-00-142-9438	No-Pest Strip	Solid	20	80 g/strip	Hang indoors; 900–1,200 ft^3 /strip

vals throughout a three- to four-month period of each trial. The results from more than 3,000 samples of air showed that in the great majority of cases (97.2 percent), concentrations were 0.1 μg/L of air or less. Values ranged from less than 0.01 to 0.24 μg/L, the higher concentrations being associated with houses closed because of the absence of the householders or with several strips being in place in the house, or both. In each trial, the dichlorvos concentration in the air rose rapidly and then fell exponentially. In temperate-area trials, the concentration was at its highest one to two weeks after placing the strips, and the geometric mean of all the values at this time was 0.04 μ/L. Three months after placement, the mean concentration was 0.01 μg/L. The two U.K. trials resulted in the same dichlorvos concentrations in air and the same rate of decline of the concentrations.

Ventilation apparently is the most important factor in determining the level of dichlorvos in the air of a room. The Australia trials were conducted in Brisbane, where houses are constructed to allow a flow of air and where doors and windows are open day and night. Concentrations of dichlorvos were low initially and quickly fell below the limit of determination. Increased ambient temperature increased the rate of emission of dichlorvos from the strip. However, in general, the increased ventilation associated with higher temperatures appeared to outweigh the increased rate of emission of insecticide, since concentrations in air tend to fall with increasing temperature. Some rooms, especially kitchens, are smaller than the volume recommended for placement of one strip. However, statistical analysis showed that initial concentrations in kitchens are no higher than in other rooms, and that the rate of decline of concentrations in kitchens is significantly higher than the rate in other rooms (Elgar, 1972).

Two trials assessed dichlorvos residues in food prepared in kitchens in which strips were placed. Samples, each of which consisted of the combined food and drink for an adult for one day, were taken at intervals during the trials. The food items were exposed and the meals prepared, including any cooking, in the way normal to the household. The residue concentrations from all the individual samples were less than 0.1 ppm. In one trial, the mean dichlorvos levels in samples taken seven, 42, and 70 days after the strips were hung were 0.03, 0.03, and 0.02 ppm, respectively. In the other trial, the mean concentrations were a

little lower—0.02, 0.02, and less than 0.01 ppm at the same times. The items of food and the way they were processed varied widely from sample to sample and also between the two trials (conducted in the United Kingdom and France, respectively). However, the residue concentration in a sample did not appear to be correlated with the food items or with the manner of processing. No relationship was observed between the volume of the kitchens used, which varied from 14 m^3 to 45 m^3, and the level of residues found in the samples (Bosio, 1972).

Malathion

General Information. Malathion is a wide-spectrum insecticide that was introduced in 1950. It is used to control sucking and chewing insects on fruits and vegetables and also to control mosquitoes, flies, household insects, and animal parasites.

The chemical identity of Malathion is shown in Table 7.13, and Table 7.14 summarizes its physical and chemical properties.

Availability and Recommended Use of Malathion During ODS/DS. Malathion was primarily used as an outdoor spray during ODS/DS to control mosquitoes and flies. Table 7.15 lists the formulations that were available.

Environmental Characteristics of Malathion. Malathion displays little persistence in soil, with rapid degradation (Howard, 1991) and reported half-lives in the field ranging from one to 25 days (Wauchope et al., 1992). It does bind moderately to some soils and could contaminate groundwater or surface water in some cases. In air, malathion is rapidly broken down by sunlight, with a reported half-life of approximately one and one-half days (Howard, 1991).

Malathion Residues. Most studies of malathion residues have been conducted on edible products; however, a few studies have focused on malathion residues on skin and fabrics. Patches of fabrics exposed to pesticide spray formulations lost substantial quantities of the chemicals within four to six hours. Fabrics

Table 7.13

Chemical Identity of Malathion

Characteristic	Information
Chemical class	Organophosphate
Chemical name	Diethyl (dimethoxyphosphinothioyl) thiobutanedioate
Trade names	Carbophos; Celthion; Cythion; Dielathion; El 4049; Emmaton; Exathios; Fyfanon; Hilthion; Karbofos; Malathion; Maltox
Chemical formula	$C_{10}H_{19}O_6PS_2$
CAS Registry number	121-75-5

Table 7.14

Physical and Chemical Properties of Malathion

Property	Information
Molecular weight	330.36
Color/form	Clear, brown to colorless liquid
Odor	May be garlic-like
Water solubility at 25°C	145 mg/L
Partition coefficient (K_{ow})	560
Soil sorption coefficient (K_{oc})	1,800
Vapor pressure at 30°C	4×10^{-5} mm Hg
EPA toxicity classification	Class III
ACGIH TLV–TWA	10 mg/m^3 (skin)
NIOSH REL–TWA	10 mg/m^3 (skin)
NIOSH REL–STEL	NA
NIOSH IDLH value	250 mg/m^3
OSHA PEL–TWA	15 mg/m^3 (total dust) (skin)
EPA IRIS RfD	2×10^{-2} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A4
EPA	NA
IARC	3

NA = not available.

Table 7.15

Formulations of Malathion Available During ODS/DS

NSN	Name	Form	Formulation (% by wt)	Unit Size	Application Method
6840-00-685-5438	E5 Malathion	Liquid	57	5-gal can	Hand sprayer
6840-00-655-9222	Malathion EC	Liquid	57	1-gal pail	Hand sprayer
6840-00-926-1481	Malathion ULV	Liquid	91	55-gal drum	ULV sprayer
6840-01-169-1842	Malathion ULV	Liquid	91	5-gal can	ULV sprayer

were cotton or 1:1 cotton-polyester blends, knitted or woven, unfinished or finished. Deposition and retention of pesticide-bearing particulates appeared to depend on mechanical restrictions related to fabric weave and on the electrokinetic potential of fabric surfaces (Serat, 1982).

In one residue study, malathion was sprayed using a truck-mounted ULV aerosol generator. Malathion concentrations were measured at selected positions on live, stationary human subjects wearing protective clothing and placed along a transect at right angles to the path of the truck. Two standing subjects were exposed downwind to the malathion spray at 7.6 m and 15.2 m. A third subject was exposed while jogging in the same direction as the spray vehicle and 1.5 m from the spray path. No significant differences ($p < 0.05$) in total

amount of malathion deposited on subjects were demonstrated. The average amounts of malathion deposited at ground level at 15.2, 30.4, and 91.2 m were not significantly different ($p > 0.05$). Malathion dermal residues were compared with the acute LD_{50} value (4,100 mg/kg) for a 70-kg adult male. Calculated malathion dermal exposures were less than the acute lethal dose for a human subject by four orders of magnitude or more (Moore, 1993).

CARBAMATES

Carbamates were originally extracted from the calabar bean, which grows in West Africa. The extracts of this bean contain physostigmine, a methylcarbamate ester (Baron, 1991). Carbamates are derivatives of carbamic acid, as OPs are derivatives of phosphoric acid. Like the OPs, carbamates as a class are not generally persistent in the environment.

The use of carbamates as insecticides began in the 1950s, and approximately 25 carbamate compounds are in use today as pesticides or pharmaceuticals. Carbamates are among the most popular pesticides for home use, both indoors and on gardens and lawns. Although not identified by OSAGWI as a pesticide of concern for Gulf War illnesses, carbaryl is perhaps the best known and most applied carbamate pesticide, used primarily for lawns and gardens. Pyridostimine bromide (PB) is also a carbamate, though not a pesticide. PB tablets were taken as a prophylactic treatment for nerve agents during ODS/DS, and a literature review of PB as it pertains to Gulf War illnesses was published as a separate volume in this series (Golomb, 1999).

Bendiocarb

General Information. Bendiocarb is a broad-spectrum insecticide used to control disease vectors such as mosquitoes and flies, as well as household and agricultural pests. Most formulations of bendiocarb are registered for general use, except for Turcam and Turcam 2.5G, which are restricted products. Perhaps the best known bendiocarb product is Ficam. Formulations include dusts, granules, ULV sprays, and wettable powders.

The chemical identity of bendiocarb is shown in Table 7.16, and Table 7.17 summarizes its physical and chemical properties.

Availability and Recommended Use of Bendiocarb During ODS/DS. Bendiocarb was primarily available during ODS/DS as a wettable powder for indoor surface treatment. According to OSAGWI, the specific product available was a 76 percent solid known as Ficam, NSN 6840-01-087-6672. Ficam can be applied indoors to control fleas, ticks, cockroaches, and stored-product pests at con-

Table 7.16

Chemical Identity of Bendiocarb

Characteristic	Information
Chemical class	Carbamate
Chemical name	2,2,dimethyl-1,3-benzodioxol-4-yl methylcarbamate; 2,3-isopropylidene-dioxyphenyl methylcarbamate
Trade names	Dycarb, Ficam, Garvox, Multamat, Multimet, Niomil, Rotate, Seedox, Tattoo, Turcam
Chemical formula	$C_{11}H_{13}NO_4$
CAS Registry number	22781-23-3

Table 7.17

Physical and Chemical Properties of Bendiocarb

Property	Information
Molecular weight	223.23
Color/form	White solid
Odor	Odorless
Water solubility at 20°C	40 mg/L
Partition coefficient (K_{ow})	50
Soil sorption coefficient (K_{oc})	570
Vapor pressure at 25°C	5×10^{-6} mm Hg
EPA toxicity classification	Class II
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	1.3×10^{-3} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	NA
IARC	NA

NA = not available.

centrations of 0.25 to 0.5 percent in water, and a 1 percent solution in water can be applied indoors to control mosquitoes.

Environmental Characteristics of Bendiocarb. Bendiocarb has low soil persistence, with half-lives in soil of from one to four weeks, depending on soil type (Worthing, 1987; Kidd and James, 1991), and may display slight mobility in some soils (Swann et al., 1983). Bendiocarb does not volatilize significantly from soil surfaces (Wright et al., 1981). Bendiocarb is degraded in solution by hydrolysis and does not accumulate in water (Kamrin, 1997).

Bendiocarb Residues. In one study, a 1 percent formulation of bendiocarb was applied in a furnished office. Airborne concentrations peaked during application at 2.7 $\mu g/m^3$; after two hours, the level decreased to 0.7 at 2.7 $\mu g/m^3$, and the levels after one and two days were 0.17 and 0.14 at 2.7 $\mu g/m^3$, respectively. Bendiocarb was deposited during application on aluminum plates (detected at concentrations of 2.1 to 3.1 ng/cm^2) and detected in floor and furniture wipe samples at concentrations of 11 to 25 ng/cm^2 (Currie et al., 1990). In another study, a 0.5 percent wettable powder suspension of bendiocarb was applied to 49 dormitory rooms. Bendiocarb was detected in air samples at 7.7 $\mu g/m^3$ on the day of application and 1.3 $\mu g/m^3$ after one day; it was not detected on the two subsequent days (Wright et al., 1981).

Methomyl

General Information. Methomyl is classified by the EPA as highly toxic to humans and is a restricted-use pesticide[1] due to its high acute toxicity to humans. It was introduced in 1966 as a broad-spectrum insecticide and was first registered in 1968. It was re-registered in 1998, with the EPA concluding that methomyl products will not pose unreasonable risk to humans or the environment when labeled and used correctly (USEPA, 1998b). Methomyl is effective both as a contact and a systemic insecticide. That is, methomyl can kill insects upon direct contact and also after absorption, especially after the insect feeds on a treated plant.

There are currently 15 methomyl products registered for a variety of uses, including agricultural use and fly control in livestock quarters, refuse containers, and commercial premises. There are no registered homeowner uses of methomyl. Methomyl can be formulated as a wettable powder, a soluble concentrate or liquid, a dust, or a solid bait.

The chemical identity of methomyl is shown in Table 7.18, and Table 7.19 summarizes its physical and chemical properties.

Availability and Recommended Use of Methomyl During ODS/DS. Methomyl was used exclusively as a fly bait during ODS/DS. According to OSAGWI, the specific product available was a 1 percent methomyl formulation known as Flytec, NSN 6840-01-183-7244. This pellet bait is packaged in five-pound cans and is intended to be used outdoors at a rate of 0.5 $lb/1{,}000\ ft^2$.

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[1]All methomyl products are restricted-use pesticides except 1 percent bait formulations (USEPA, 1998b).

Table 7.18

Chemical Identity of Methomyl

Characteristic	Information
Chemical class	Carbamate
Chemical name	S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate
Trade names	Acinate, Agrinate, DuPont 1179, Flytek, Kipsin, Lannate, Lanox, Memilene, Methavin, Methomex, Nudrin, NuBait, Pillarmate, SD 14999
Chemical formula	$C_5H_{10}N_2O_2S$
CAS Registry number	16752-77-5

Table 7.19

Physical and Chemical Properties of Methomyl

Property	Information
Molecular weight	162.2
Color/form	Colorless to white crystalline solid
Odor	Slight sulfurous
Water solubility at 25°C	10 g/L
Partition coefficient (K_{ow})	3.98
Soil sorption coefficient (K_{oc})	51, 72, 160 (depending on reference)
Vapor pressure at 25°C	5.0×10^{-5} mm Hg
EPA toxicity classification	Class I
ACGIH TLV–TWA	2.5 mg/m^3
NIOSH REL–TWA	2.5 mg/m^3
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	2.5×10^{-2} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A4
EPA	E
IARC	NA

NA = not available.

Propoxur

General Information. Propoxur was introduced in 1959 as an insecticide, and it was first registered in the United States in 1963. Like methomyl, it has both contact and systemic activity against insects and is used on a variety of pests in both agricultural and non-agricultural applications. Propoxur is a general-use pesticide, although some formulations may be for professional use only.

Propoxur is characterized by a fast knockdown and a long residual effect, which makes it a popular choice for pest control. It is used primarily indoors. Propoxur is available in a variety of formulations, including emulsifiable con-

centrate, wettable powder, dustable powder, granules, aerosol generator, smoke generator, and baits.

Generally, propoxur is moderately toxic to mammals when ingested and slightly toxic in inhalation and dermal exposures. Mild cases of poisoning were noted during WHO-sponsored, wide-scale spraying of propoxur for malaria control. Applicators who used propoxur on a regular basis showed a pronounced daily fall in whole blood cholinesterase activity and a distinct recovery after exposure ceased. No adverse cumulative effects were demonstrated (ACGIH, 1986, p. 499).

The chemical identity of propoxur is shown in Table 7.20, and Table 7.21 summarizes its physical and chemical properties.

Availability and Recommended Use of Propoxur During ODS/DS. During ODS/DS, propoxur (Baygon) was used indoors as a crack and crevice treatment to control pests such as cockroaches; it was also sprayed on building surfaces and screens to control outdoor pests (Table 7.22).

Environmental Characteristics of Propoxur. Propoxur is generally not known to be strongly absorbed by soil and is readily degraded in water (it has a half-life of from one day to one week). Propoxur biodegradation in soil and water is rapid, particularly at high temperatures. On the basis of propoxur's vapor pressure and water solubility, its volatilization from water is considered negligible. It hydrolyzes in water at a rate of 1.5 percent per day in a 1 percent aqueous solution at pH 7.0 (USEPA, 1988b). Propoxur degrades rapidly at more alkaline pH values.

The field half-life of propoxur has been reported to be 14 to 50 days. It has a low affinity for soil binding and may therefore be mobile in many soils (Wauchope et al., 1992). A USEPA study found virtually no loss of propoxur from silty loam

Table 7.20

Chemical Identity of Propoxur

Characteristic	Information
Chemical class	Carbamate
Chemical name	2-(1-methylethoxy)phenyl methylcarbamate; o-isopropoxyphenyl N-methylcarbamate
Trade names	Aprocarb, Bay 39007, Bay 9010, Baygon, Bayer 39007, Bifex, Blattanex, Brifur, Bolfo, BO Q 5812315, ENT 25671, Invisi-Gard, OMS 33, PHC, Pillargon, Prentox Carbamate, Propogon, Propyon, Rhoden, Suncide, Sendran, Tendex, Unden, Undene
Chemical formula	$C_{11}H_{15}NO_3$
CAS Registry number	114-26-1

soil six months after application, but 25 percent of applied propoxur (Baygon) was lost from sand after 100 days (USEPA, 1988). Other studies have shown that propoxur is mobile in soils with more organic content as well (e.g., silty clay, silty loam, and sandy loam) (Kamrin 1997).

Table 7.21

Physical and Chemical Properties of Propoxur

Property	Information
Molecular weight	209.24
Color/form	White to cream or tan crystalline solid
Odor	Odorless to faint characteristic
Water solubility at 25°C	1,750 mg/L
Partition coefficient (K_{ow})	1.4
Soil sorption coefficient (K_{oc})	30
Vapor pressure at 20°C	3×10^{-6} mm Hg
EPA toxicity classification	Class II for oral exposures; Class III for dermal and inhalation exposures
ACGIH TLV–TWA	0.5 mg/m^3
NIOSH REL–TWA	0.5 mg/m^3
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	4×10^{-3} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	A3
EPA	NA
IARC	NA

NA = not available.

Table 7.22

Formulations of Propoxur Available During ODS/DS

NSN	Name	Form	Formulation (%); Application	Unit Size	Application Method
6840-01-033-2623	Baygon	Wettable powder	70; suspension of 2 oz/gal to treat buildings and screens	5-lb bag	Hand spray gun
6840-00-180-6069	Baygon	Oil solution	1; crack and crevice treatment	1-gal can	Hand spray gun
6840-01-027-3865	Baygon	Liquid	14.7; crack and crevice treatment	1-gal can	Hand spray gun or power sprayer

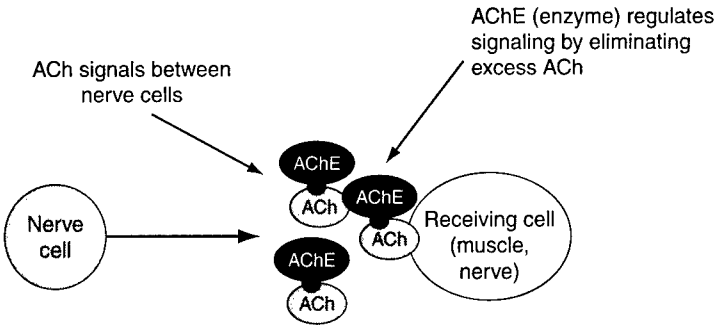
Source: Provided by OSAGWI.

Propoxur Residues. The EPA has estimated a cancer risk of 4.5×10^{-7} for applicators of crack and crevice treatments (USEPA, 1997). (Residential cancer risks of less than 1×10^{-6} are considered not to be of concern.) It should be noted that this estimation is based on a suite of assumptions regarding propoxur application and exposure to target individuals. While these assumptions were made conservatively, they should be reviewed if unique information regarding exposures during the Gulf War is discovered.

Following crack and crevice treatment, individuals can be exposed to propoxur via inhalation or dermal contact with residue. In its approval of residue studies following crack and crevice treatments, the EPA pooled concentration data to yield an average air concentration of 5.1 μg propoxur/m^3 over a one-year period which included a 64-ounce treatment of a 1.1 percent propoxur solution by weight (total of 0.73 ounce) for annual cleanout treatment as well as 11 treatments of 16 ounces of a 0.5 percent propoxur solution by weight (a total of 0.083 ounce per treatment) (USEPA, 1997). In another study, the airborne concentration of propoxur after application as a 1.1 percent emulsion to a 61.2-m^3 dormitory room whose approximate temperature and humidity were 25°C and 60 percent was 15.4 μg propoxur/m^3. After one, two, and three days, the levels declined to 2.7, 1.8, and 0.7 μg propoxur/m^3, respectively (Wright et al., 1981). Propoxur was also detected in the indoor air of seven of nine households in a pilot project of pesticide exposure. The concentrations in areas of high household activity (e.g., kitchens) ranged from none detected to 0.0039 μg/m^3, with a mean of 0.042 μg/m^3 (Lewis et al., 1988).

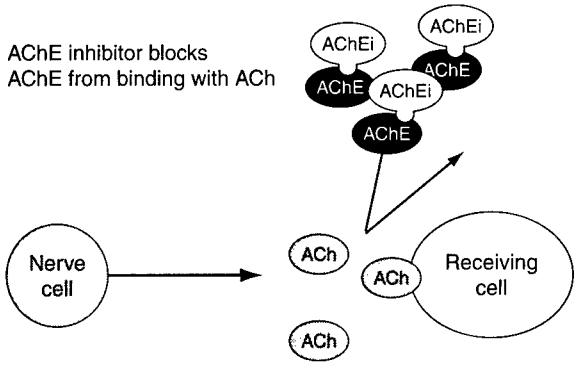
POTENTIAL HEALTH EFFECTS OF ORGANOPHOSPHATES

OP (like carbamate) agents act by binding to, and inhibiting the normal action of, acetylcholinesterase (AChE), an enzyme. Acetylcholine (ACh) is a major neurotransmitter, or nerve-signaling chemical, that acts as a signaling chemical both in the brain and elsewhere in the body; for example, it is the main signaling chemical used by nerves to tell muscles to contract. AChE breaks down (metabolizes) ACh in the synapse, the area where a nerve sends signals to another nerve or to a muscle (see Figure 7.1). When AChE is inhibited by an OP, an excessive accumulation of ACh occurs in the synapse, followed by excessive binding of ACh to the receptors on the receiving cell (see Figure 7.2). Consequently, cells are excessively stimulated. The increase in ACh action leads to symptoms characteristic of increased ACh activity at peripheral and, to varying degrees, central ACh receptors, which fall largely into two classes, nicotinic and muscarinic.



ACh is important in muscle action, pain, memory, and sleep.

Figure 7.1—Normal Nerve Signals



Excess ACh accumulates, signals occur when they should not; results may include muscle twitching, paralysis, seizures.

Figure 7.2—Effect of AChE Inhibitors Such as OPs

Nicotinic effects in the periphery, consisting of effects at the neuromuscular junction as well as at other nicotinic sites, include fasciculations and muscle contractions, muscle pain, generalized weakness and fatigue, tachycardia, hypertension, hyperglycemia, pallor, paresthesias, and, rarely, mydriasis (Minton and Murray, 1988; Leveridge, 1998).

Muscarinic effects in the periphery include secretions from glands and contraction of smooth muscles, leading to such symptoms and signs as lacrimation (secretions from tear ducts), hypersalivation, diaphoresis (sweating), rhinorrhea (runny nose), bronchorrhea (bronchial secretions), bronchial constriction,

cyanosis, nausea, vomiting, abdominal cramps and diarrhea (from increased peristalsis and increased intestinal secretions), urinary urgency or incontinence (from contractions of sphincteric muscles), miosis, blurred vision, bradycardia, heart block, hypotension, dyspnea (shortness of breath), and pulmonary edema (Minton and Murray, 1988; Leveridge, 1998).

Central muscarinic and nicotinic effects include insomnia and sleep abnormalities, headaches, dizziness, effects on mood (depression, anxiety), effects on personality (aggressiveness, irritability, and paranoia), effects on cognition (confusion, enhancements and reductions in measures of attention, concentration, memory, learning, and psychomotor speed), tremor, ataxia, dysarthria, hypotension, respiratory depression or arrest, convulsions, and coma (Devinsky et al., 1992; Minton and Murray, 1988; Leveridge, 1998). In addition, AChE inhibitors may affect thermoregulation and response to stress.

Acute Effects

Symptoms that occur acutely with OP (and carbamate) toxicity can span a range from mild tremors to more severe muscle contractions, impaired cognition, dizziness, shortness of breath, and vomiting. In severe cases, respiratory failure and death can result. The severity of symptoms is related to the amount and route of exposure. The literature contains no systematic reports of acute toxicity resulting from any pesticide exposures during ODS/DS; however, it is conceivable that mild symptoms related to such exposures could have occurred and medical care was not sought, or the symptoms may have been attributed to other factors. For this reason, this report focuses primarily on chronic exposures and long-term effects.

Acute toxicity for both OP and carbamate poisoning may be complicated by ventricular arrhythmias, CNS depression, seizures, or respiratory failure; and relapse may occur after seemingly successful treatment (Bardin et al., 1994). Additional problems with acute toxicity that have been described less frequently include renal failure, which may be associated with proteinuria (Wedin et al., 1984; Albright et al., 1983), and pancreatitis, which has been reported to occur with exposure to AChE-inhibiting pesticides—most commonly, OPs—in adults and children and may be painless and go undetected. Hyperamylasemia is particularly common (Weizman and Sofer, 1992; Dagli and Shaikh, 1966; Dagli et al., 1981; Dressel et al., 1979; Lankisch et al., 1990; Lee et al., 1997; Marsh et al., 1988; Moore and James, 1981).

Most of what is known about symptoms associated with acute exposures to pesticides, including OPs, comes from studies of patients who were involved in accidental exposures or mishandling/misapplication of pesticides. For

example, Saadeh et al. (1996) evaluated clinical manifestations of 70 adult patients (33 males, 37 females) in North Jordan who were admitted to a teaching hospital for acute carbamate or OP poisoning associated with accidents, suicide attempts, or occupational exposures. Clinical manifestations reported are listed in Table 7.23.

OPIDN and Intermediate Syndrome. The specific cases of OP-induced delayed neuropathy (OPIDN)—also called OP-induced delayed polyneuropathy (OPIDP)—and intermediate syndrome will be discussed only briefly. Although each is a well-described, somewhat delayed phenomenon, both are generally considered to require significant acute exposure, which would be expected to have occurred very seldom during ODS/DS. Moreover, the symptoms have only passing relevance to those being reported by ill PGWV. However, they do provide an example of delayed, and in one instance long-lasting, illness whose onset is precipitated by, but not tied to drug levels of, AChE-inhibiting agents.

OPIDN is a form of delayed clinical and pathological response to OPs. There is a chronic central and peripheral distal axonopathy affecting both sensory and motor fibers, with a secondary myelinopathy leading to clinical symptoms consisting of a progressive phase (primarily a peripheral neuropathy) followed

Table 7.23

Clinical Manifestations Following Acute Carbamate or OP Poisoning (n = 70)

Clinical Effect	Prevalence Among Patients (%)
Miosis	86
Nausea and vomiting	73
Excessive salivation and bronchial secretions	73
Headache and dizziness	63
Fever	49
Abdominal pain or cramps	47
Muscular twitching and fasciculation	44
Pulmonary edema	40
Sinus tachycardia	36
Coma	29
Sinus bradycardia	28
Diarrhea or urinary incontinence	24
Hypertension	22
Blurred vision	21
Hypotension	17
Fits	16
Tremors	13
Hallucination	10
Respiratory muscle paralysis	3

Source: Saadeh et al. (1996).

by a stationary phase and an improvement phase. Longer-diameter motor and sensory fibers may or may not be more susceptible (Jamal, 1995). In the progressive phase, there is a distal symmetric sensory and motor neuropathy that affects primarily the lower limbs. Initial pain, burning, and tingling sensations of the lower extremities may later lead to hypoesthesia in a stocking or stocking-and-glove distribution. Weakness of the legs may spread to the hands, and foot drop, steppage gait, ataxia, a positive Romberg sign, and even possibly paraplegia or quadriplegia (bilateral flaccid paralysis) may occur in severe cases. In the stationary phase, lasting from three to 12 months after symptom onset, the sensory symptoms may disappear, but weakness persists. In the improvement phase, from six to 24 months after onset of neurological deficits, improvement occurs in reverse order to symptom onset. Typically, onset follows significant acute OP toxicity. There is some question about whether more-subtle cases of OPIDN may be more common than previously thought (Jamal, 1995; Schaumburg and Berger, 1993).

Symptoms typically follow exposure to selected OPs by one to three weeks (Abou-Donia, 1981; Abou-Donia and Lapadula, 1990; Jamal, 1995). Apparently complete recovery may occur in mild cases. The likelihood of recovery has been estimated at less than 2 percent in severe cases (Geoffroy et al., 1960; Minton and Murray, 1988); hands may show great improvement, but paralysis below the knees may remain. Later stages of neurological deficit involve central rather than peripheral lesions in the spinal cord. These lesions are unmasked as peripheral neuropathy abates and are characterized by spasticity (increased muscle tone) and exaggerated knee jerk (Abou-Donia and Lapadula, 1990). Chronic neuropsychological effects have also been reported to occur (Lotti, 1992; Karczmar, 1984).

Induction of OPIDN is thought to be related not to AChE inhibition, but to phosphorylation of the enzyme neurotoxic esterase, or neuropathy target esterase (NTE), a membrane bound carboxylesterase, followed by "aging" of the OP-NTE complex. While OPs generally inhibit AChE, only a selected subset also inhibit lymphocyte and brain NTE, and inhibition of NTE has been useful in predicting which agents can produce OPIDN (Barrett and Oehme, 1985; Gordon et al., 1983; Lotti and Johnson, 1978; Lotti and Moretto, 1986). It has been thought that induction of OPIDN requires at least 70 percent inhibition of NTE. Not all OPs that inhibit NTE produce OPIDN, and, like carbamates, those that do not typically produce it may protect against it if administered before a neurotoxic OP exposure (Pope et al., 1993; Pope and Padilla, 1990). Not all animals are similarly susceptible; for example, cats, primates, and hens develop OPIDN, while rats are relatively refractory. "Non-neuropathic" OPs and carbamates may potentiate OPIDN if administered after the neuropathic OP, or may even produce it in animals who would not have been susceptible from the neuro-

pathic OP exposure alone (Pope et al., 1993; Pope and Padilla, 1990). Moreover, as noted in the section on carbamates, delayed neuropathy has been reported following carbamate exposure without known OP exposure.

Intermediate syndrome is a delayed neurotoxic condition (also called Type II paralysis) that has only recently been defined. It occurs after the acute OP cholinergic crisis, but before the development of OPIDN—typically one to four days after acute poisoning (Senanayake and Karalliedde, 1987). The main symptoms are a proximal neuropathy and muscle weakness (e.g., in the neck flexors, motor cranial nerves, proximal muscles of the limbs, and respiratory muscles), with recovery usually within several weeks (Jamal, 1995; Leon et al., 1996; Mani et al., 1992). Respiratory insufficiency or ventilatory failure may result from paralysis of the respiratory muscles, and artificial ventilation may be required. Deep tendon reflexes may be absent. A number of OPs have been implicated, including fenthion, methyl-parathion, parathion, and dimethoate; and while the syndrome may occur more commonly with certain compounds—perhaps those with higher lipid solubility—it is not confined to a few distinct compounds (De Bleecker, 1993). Recovery usually occurs at between four and 18 days. The necrotizing myopathy seen with AChE inhibitors has been suggested as a cause (Senanayake and Karielledde, 1987), as has persistent AChE inhibition (De Bleecker, 1993)

Other Persistent Effects Following Acute Exposure. In some cases, acute exposure to OPs has been associated with effects manifesting from days to years later. For example, Markowitz et al. (1986) compared 22 seamen accidentally exposed to a cloud of malathion from a nearby overheated tank with 21 seamen controls from a distant tanker. The subjects were interviewed 12 days after exposure for symptoms, using a medical review of body symptoms and a "demoralization" scale reflecting psychological symptoms of distress. For 17 of 18 symptom classes, the OP-exposed seamen reported symptoms more frequently than did the control seamen by at least a factor of two ($p < 0.001$, sign test). The symptoms are listed in Table 7.24 in descending order of frequency of occurrence.

Thrasher et al. (1993) reported persistent symptoms of fatigue, headache, joint and muscle pain, memory problems, upper and lower respiratory problems, GI disturbance, dizziness, atopy, and antibiotic sensitivity from one to four-and-one-half years after reported chlorpyrifos exposure in 12 subjects.

Twenty-nine lettuce harvesters who were exposed to the OP mevinphos and presented to the emergency room for acute cholinergic symptoms were followed for 12 weeks (Coye et al., 1986). Initial symptoms of headache, eye irritation, blurred vision, and pruritus persisted at least 10 weeks in some of the harvesters. Similarly, Tabershaw and Cooper (1966) followed up on 114 of 232 pa-

Table 7.24

Symptom Rates in Malathion-Exposed Subjects

Symptom Class	Risk Ratio	% of Cases
Head (headache, dizziness)	3.0**	73
GI	5.9**	59
Nose or throat	3.1	59
Sleep problems	2.1	50
Abdominal (pain, nausea)	2.1	50
Energy	2.3	43
Eyes/vision	4.1*	41
Chest or respiratory (chest pain, shortness of breath, cough)	2.7	38
Mouth/lips/teeth	2.6	36
Muscle/joint pain or neuropathy	2.4	33
Appetite	8.6**	32
Urinary	3.2	32
Skin/hair	2.7	27
Motor function	3.8	19
Heart rhythm (pound, skip)	14:0 (undefined)	14
Temperature (fever/chills)[a]	10:0 (undefined)	10
Genitals or sexual function	5:0 (undefined)	5

Source: Markowitz et al. (1986).

*$p < 0.05$.

**$p < 0.01$.

[a]The context of fever and chills is extremely important in interpreting this finding. Fever and/or chills during infectious disease is arguably not disruption of thermoregulation, but rather a normal response. Increased fever and chills could, therefore, signal diminished resistance to infectious disease—not altered thermoregulation. On the other hand, unexplained fevers, etc., might signal altered thermoregulation. Malathion-exposed seamen, evaluated days after exposure, experienced increased fever and chills, and there was no direct evidence to suggest that infection was present. Increased fever and chills could also result from susceptibility to occult, undiagnosed infection. Changes in immune function could be theorized to lead to such increased susceptibility, perhaps selectively to certain viral, parasitic, and intracellular bacterial infections that may relate to changes in T-helper cell cytokine profiles.

tients who had experienced acute OP toxicity three years earlier. The duration and nature of the OP exposures were not defined. Nine percent reported persistent headaches and anxiety three years later, and many cited blurred vision. The vision problems were attributed by the authors to presbyopia, but no control rates were given to support this attribution. Few long-term sequelae were reported. Symptoms lasting longer than six months were reported by 38 percent of the subjects.

Thirty-six male Nicaraguan agricultural workers 15 to 44 years of age at the time of hospitalization for OP intoxication were compared with male controls (a close male friend or sibling never treated for pesticide poisoning and matched

by age, within five years, to each exposed participant) approximately two years following the acute toxicity episode (Rosenstock et al., 1991). Ongoing lower-level OP exposure was not excluded, and the duration of exposure was not reported. Symptoms related to CNS function were assessed by a validated test of self-reported difficulties in memory and concentration, along with headache, fatigue, depression, and irritability (Scandinavian questionnaire, $p < 0.01$) (Hogstedt et al., 1984). It was observed that "the exposed group did much worse than the control group on all neuropsychological subtests." Findings were adjusted for vocabulary score, considered moderately resistant to cortical insult. Differences in neuropsychological performance could not be explained by other factors examined.

Midtling et al. (1985) studied cauliflower workers who experienced acute poisoning by OP insecticides mevinphos (Phosdrin) and phosphamidon (Dimecron). The workers had begun work tying leaves over the heads of the plants only six hours after the field had been sprayed. Sixteen such workers were followed in weekly clinics with interviews and plasma and red blood cell (RBC) cholinesterase levels. Comparatively non-persistent symptoms (i.e., they had typically resolved by 10 weeks) included nausea, dizziness, vomiting, abdominal pain, ataxia, and night sweats or insomnia. Symptoms that persisted in at least three of the 16 subjects at 10 weeks or more included blurred vision/vision disturbance (56 percent), headache (25 percent), anxiety (41 percent), weakness, and anorexia. Symptoms persisted for up to 10 weeks, varying by symptom and individual. Six of the subjects initially had RBC AChE values within the normal laboratory range, but follow-up testing showed activity to have been significantly inhibited.

Chronic Effects

Chronic health effects are of greater relevance to Gulf War illnesses than are acute effects. In addition, most reports of acute effects center on large exposures with severe acute debility, which is not known to have been reported following pesticide exposure during ODS/DS. As with other pesticides, most of what is known about the effects of persistent OP exposure in humans is based on observational studies. These studies are usually focused on occupational exposures, and they usually involve a mixture of pesticides and possibly other compounds. They often assess the symptoms of a study group that is exposed to pesticides seasonally. Further, there is often a combination of acute and chronic exposures and effects, and this combination is frequently undefined. For example, a seasonal agricultural worker who mixes and sprays pesticides is almost certainly exposed chronically but also risks acute exposures to higher concentrations because of accidents during mixing, loading, and handling.

For example, in a study of fenthion (OP) sprayers presumed to be exposed chronically and seasonally, serum AChE was found to be significantly inhibited in the exposed group ($p < 0.01$), making it difficult or impossible to distinguish the effects of acute inhibition from chronic effects (Misra et al., 1994). In that study, 32 sprayers with a mean age of 32.1 years (range = 19 to 55 years) and a mean exposure of 10.5 years (range = one to 14 years) were compared with 25 non-exposed hospital employees matched for age (mean 30.0, range = 18 to 50 years), sex, educational status, and socioeconomic status. Significant deficits were observed in the following neuropsychological evaluations of the sprayer group:

- Benton visual retention test ($p < 0.01$)
- Preservation—"the most important abnormality" ($p < 0.01$)
- Memory quotient ($p < 0.05$). Impaired subscales included
  - —Visual reproduction subscale ($p < 0.01$)
  - — Logical memory subscale ($p < 0.05$)
  - — Associate learning ($p < 0.05$)
  - — Alexander's Passalong Test ($p < 0.05$)
  - — Cz P3 latency ($p < .0.01$)
  - — Fz P3 latency ($p < 0.02$)

In a study that compared 57 OP-exposed male fruit-tree farmers with 42 male controls, Fiedler et al (1997) found slower reaction times among the OP-exposed farmers. This group had significantly slower reaction times with the dominant hand than did the control group, which included hardware-store owners and cranberry/blueberry growers thought to be unexposed to OPs. The fruit-tree farmers were exposed seasonally to OPs and were "without evidence of an acute poisoning episode." Symptoms were not assessed, and the recency of last exposure was not provided, so recent OP exposures could not be excluded.

In another examination of 300 subjects exposed for years to mixed pesticides, including OPs, the longest exposures (>20 years) were associated with higher frequencies of weeping ($p < 0.05$) and irritability ($p < 0.001$) than were found in 300 control subjects (Amr et al., 1993). No additional values were reported for other symptoms in the long-term-exposure cases. AChE inhibition was widely present in the exposed subjects, indicating that many were exposed to OPs and/or carbamates, but information on other exposures was not provided.

Stephens et al. (1995) compared 145 male sheep farmers in the United Kingdom who were exposed to OPs used as sheep dips with 143 quarry workers who were presumed to be non-exposed. Licensed OP sheep dips in the United Kingdom contain either diazinon, a mixture of diazinon and chlorfenvinphos, or propetamphos as the active ingredient. Episodes of acute toxicity were neither required nor excluded in study participants, whose ages ranged from 16 to 65 years, and symptoms were not reported. While scores on the subjective memory questionnaire (evaluating perception of memory function) did not differ between the groups ($p = 0.39$), those who reported greater pesticide exposure history also displayed greater decrement in syntactic reasoning performance ($F = 5.54$, $p < 0.0001$). Further, for the general health questionnaire, reporting of at least five symptoms, regarded as indicating "vulnerability to psychiatric disorder," was more common among sheep dippers than among controls (OR = 1.5, 95 percent CI = 1.31–1.69, $p = 0.035$).

In another observational study, 146 U.K. sheep farmers were compared with 153 non-exposed quarry workers; the 10 most symptomatic and 10 least symptomatic farmers were compared with each other immediately after dipping and with 10 of the quarry workers (the selection process was not described) several months later on a standardized neurological exam (Beach et al., 1996). Some significant differences were observed between the two farmer groups. The symptomatic group had significantly smaller mean calf circumference ($p = 0.033$), an increased two-point discrimination distance in the hand (22 mm vs. 13 mm, $p = 0.011$), and an increased two-point discrimination distance in the foot (34 mm vs. 10 mm; $p < 0.001$). There was no significant difference in OP exposure between the two groups of sheep farmers. The authors suggest that "some neurological changes, albeit relatively subtle, had occurred as a consequence of long-term exposure to OP sheep dip at concentrations which had never induced sufficient symptoms that medical attention was sought." More specifically, the data suggest that this may occur selectively in a susceptible subset that may be identified by more pronounced acute changes on AChE-inhibitor exposure.

A prospective cohort study of Indonesian farmers and professional sprayers exposed to OPs resulted in a comprehensive list of symptoms putatively associated with seasonal OP exposure (see Table 7.25) (Kishi et al., 1995). Subjects were examined during the spraying season ($n = 904$) and the off-season ($n = 1,392$). (The different sample sizes imply that the samples were not identical in each test.) A trend was seen between neurobehavioral signs and symptoms and the use of multiple OP and carbamate pesticides. Tests of trends were positive for the factors shown in Table 7.26 (i.e., the factors were significantly linked to symptom reporting).

Table 7.25

Symptom Rates and Relative On-Season and Off-Season Risks for Indonesian Farmers Engaged in OP Pesticide Spraying

Symptom Class	Spray Season, % (n = 904)	Off-Season, % (n = 1,392)	Relative Risk	95% CI
Neurobehavioral				
Fatigue	60.2	20.4	3.0	2.6–3.3
Dizziness	20.8	4.1	5.1	3.8–6.7
Insomnia	16.8	2.4	7.1	4.9–10
Blurred vision	15.5	4.2	3.7	2.7–4.9
Flushed face	13.9	0.3	48	18–131
Headache	13.2	4.9	2.7	2.0–3.6
Salivation	13.1	0.8	17	9–30
Excess sweating	3.7	0.5	7.3	3.2–16
Pallor	2.9	0.7	4.2	2.2–8.2
Hand tremor	2.0	0.2	9.2	2.7–31
Twitching eyelids	1.5	0.3	5.4	1.8–16
Staggering	0.9	0.1	12	1.5–98
Irritability	0.3	0.9	0.3	NS
Loss of consciousness	0	0	NA	NA
Intestinal				
Nausea	10.8	1.7	6.6	4.2–10
Queasiness	5.4	1.1	5.0	2.8–8.9
Belly pain	3.1	1.6	1.9	NS
Constipation	1.9	0.5	3.8	NS
Vomiting	0.7	0	Undefined	
Diarrhea	0.3	0.5	0.6	NS
Respiratory				
Dry throat	29.9	0.8	38	21–69
Difficulty breathing	18.5	2.0	9.2	6.2–14
Chest pain	13.6	2.7	5.1	3.6–7.3
Sore throat	5.2	1.1	4.8	2.7–8.6
Cough	4.4	6.2	0.7	NS
Runny nose	1.9	4.4	0.4	NS
Epithelial/mucosal surfaces				
Stinging eyes	15.2	0.8	19	10–35
Itchy skin	0.3	4.6	2.0	1.5–2.8
Red eyes	7.3	2.2	3.3	2.2–5.0
Burning nose	6.5	0	Undefined	
White rash and scaling	5.4	0.9	6.3	3.4–12
Burning eyes	5.1	0.1	35	9–145
Itchy eyes	3.7	0.1	25	6–105
Blisters	1.5	0.3	5.0	NS
Red skin	0.8	0.3	2.6	NS
Eye discharge	0.7	0.9	0.8	NS
Burning tongue	0.6	0.1	6.0	NS
Abraded skin	0.3	0	Undefined	
Muscle				
Muscle stiffness	54.0	18.6	2.9	2.6–3.3
Muscle weakness	22.8	13.5	1.7	1.4–2.0
Muscle cramps	1.8	0.7	2.6	NS

NA = not available; NS = not significant.

Table 7.26

Factors Significantly Linked to Symptom Reporting in Indonesian Farmers Engaged in OP Spraying

Factor	p-Value for Trend
Sprayed since previous week	0.00000
Wore clothes unwashed since previous spray	0.00000
Used bottle to mix pesticide "cocktail"	0.00000
Feet wetted when pouring solution	0.00000
Body wetted by solution	0.00000
Shirt soaked with solution	0.00000
WHO hazard grade IB/II (% of pesticides)[a]	0.0039
Multiple use of hazardous pesticides[b]	0.0001

[a]Proportion of pesticides used that are classified as highly hazardous or moderately hazardous.
[b]Two or more grade IB/II pesticides (OP and carbamates) mixed together.

While some study designs compare exposed and non-exposed populations, others employ a longitudinal study design of pre- and post-season observations. In one such study in Israel, neurobehavioral tests were administered to 90 subjects (51 occupationally exposed, 39 non-exposed) before and after the pesticide spraying season (Richter et al., 1992). Workers had significantly ($p < 0.05$) worse ratios of peak- to post-season test scores than non-worker residents in the same "exposed" kibbutzim (see Table 7.27).

Some cases involving household pesticide use also provide information about the nature of OP effects following prolonged exposure. Richter et al. (1992) reported that four family members were experiencing fatigue, sleep problems, irritability, vomiting (infant), runny nose (infant), dizziness, headache, and chest heaviness four and one-half months after their apartment was treated commercially with diazinon. Diethylphosphate, a urinary metabolite, was also detected in the urine of symptomatic household members four and one-half

Table 7.27

Difference Between Peak- and Post-Season Test Score Ratios of Occupationally Exposed and Non-Exposed Israelis

Test	Difference Between Scores of Exposed and Non-Exposed Subjects (%)
Digit symbol (scaled score)	–3.3
Digit span backwards	–10.3
Scaled score (test for short-term memory)	–10.6
Symptoms (depression)	–4

months after the diazinon application. Swabs of wall surfaces revealed residual concentrations (126 to 1,051 $\mu g/m^2$) much higher than ambient air concentrations (2.5 to 0.1$\mu g/m^3$) 0 to 56 days after indoor spraying. A coat and skirt that emitted an odor were also found to be contaminated. The 30-year-old mother and an infant were most affected, although symptom persistence was not reported.

Kaplan et al. (1993) presented a similar case series of residential exposure to chlorpyrifos resulting in such symptoms as cognitive slowing, cognitive problems, and sensory neuropathy weeks to months after application. Again, symptom persistence was not reported.

As discussed above, it is often difficult to attribute specific effects to either acute or chronic pesticide exposures. This difficulty can be due to inaccurate or incomplete reporting, misattribution of symptoms, or a variety of other factors. In many studies of persistent effects, acute toxicity is used to select the study group. In some cases, acute exposures great enough to cause illness (e.g., poisonings) clearly implicate the causative agent. Pesticide exposures of these types were not reported to have occurred during ODS/DS. Therefore, studies of chronic effects in the absence of acute toxicity may be of greater relevance.

Richter et al. (1992) assessed symptoms in 11 Israeli ground-crew workers who were exposed to OP and other pesticides and displayed low-level cumulative systematic reductions in ChE activity, compared with 13 controls. Test results (electroneuromyography) indicated lower peak amplitude in sural but not peroneal nerve (mean $\pm$SD = 10.1$\pm$4.0 vs. 14.0$\pm$2.6 mV, $p < 0.05$). The authors comment, "In all groups, evidence of exposure-illness associations was found even though persons with acute poisoning were not seen."

The same 11 subjects, age 24 to 36 years, were compared with 13 male kibbutz residents, age 24 to 41 years, living further than 1 km from a sprayed field (Richter et al., 1992). The ground-crew workers had higher frequencies (relative risks > 2) of fatigue, dizziness, concentration problems, confusion, memory problems noted by others, depression, palpitations, sleep problems, weakness in extremities, tingling in extremities, headaches at work, nausea, vision problems, cramps, breathing problems, uncontrolled sweating, "annoyance from odors at work," and urinary frequency. Controls may have been exposed, but at a lower level. Workers with past self-reported episodes of acute illness (n = 20) did no worse on tests than an age-sex-education-matched comparison group; and those who "spent their youth" in the kibbutz ("possible childhood exposure") did no worse than age-sex-education-job matched residents who joined the kibbutz after age 20 (<10 years of seasonal exposure); in fact, the former group scored higher on the Benton Visual Retention Test and the Trails 2 Test. However, strong conclusions cannot be drawn because there may be relevant

differences in these populations. Those who remained in the kibbutz may have self-selected for resilience to pesticides and/or less exposure; people who chose to move from a kibbutz may have differed from those who remained in one. In addition, the samples are too small to overcome large variability in normal values. Analogously, another cited study showed that in-season variations in ChE activity were well within normal limits in 26 workers and 11 residents exposed to spray drift and seven residents who were not exposed. However, additional data showed that reductions were greater in workers and exposed residents than in unexposed residents.

An observational NIOSH study compared 45 male pesticide workers who had prior histories of documented ChE inhibition below worker removal thresholds, but no evidence of frank poisoning, with 90 subjects who were not "expected to have current cholinesterase inhibition" but were not otherwise defined, on a series of neurological tests, including neurobehavioral tests, nerve conduction tests, vibrotactile sensitivity tests, tests of postural sway, and a clinical exam (Ames et al., 1995). It was not stated whether the controls also worked with pesticides. Acute toxicity was not reported and was, in fact, used as an exclusion criterion. The study group did not perform significantly worse than the control group on any of 27 tests performed. Tests included nerve conduction velocity and amplitude (median motor and sensory, ulnar sensory, peronial motor, sural sensory); vibration (finger, toe); neurobehavioral (tapping, hand-eye, simple reaction time, sustained attention, digit-symbol, pattern memory, serial digit); mood (tension, depression, anger, fatigue, confusion); and motor coordination (pursuit aiming, Santa Ana dexterity, postural sway). Because of the nature of the study group and the fact that prior pesticide exposure in the control group was not defined, the results support the observation that degree of cholinesterase inhibition does not correlate well with presence (or development) of neurobehavioral abnormalities. The choice of subjects with no clinical symptoms despite low ChE levels may also have biased the subset toward the most physiologically resilient.

Genetic Effects

One study of 13 malathion-exposed workers in the Southern California Mediterranean fruit fly eradication program, in which malathion was used as ground treatment, examined micronucleus formation and mutation frequencies assessed by the glycophorin A (GPA assay). The workers were compared with only four controls, who supervised or organized crews and may therefore not have been unexposed (Windham et al., 1998). In a 1992 pilot project, the mean micronuclei level appeared higher in lymphocytes of exposed workers (20.1±7.1 vs. 14.3±7.2, $p = 0.09$), but the finding did not reach significance. In the 1993 season, an additional 24 workers and 11 controls (primarily staff "not

directly involved in malathion application") were recruited. Neither the first nor the second cohort showed a higher level of micronuclei than did the presumably less-exposed control group; nor did the pooled total (means = 17.8±7.2 vs. 18.5±6.3); nor did they after adjustment by multiple regression. Glycophorin A variant frequency was not shown to be associated with malathion exposure. Of note, 29 percent of the "office workers and supervisors" who served as controls reported having been exposed to pesticides in the previous six months. In addition, 21 of the applicators had also been exposed to diazinon and dibrom.

Another study was initiated when the mother of a 12-year-old girl asked whether her child's residential exposure to OPs could have genetically affected her ability to reproduce (Lieberman et al., 1998). Cytogenetic studies showed that lymphocytes of both the mother and the child were abnormal, and on the basis of this finding, a group of residentially exposed, OP-pesticide-poisoned subjects were evaluated. All had a clear temporal relationship between documented application of pesticides and classic OP pesticide poisoning. Eight subjects, ranging from 12 to 62 years of age, all reportedly in good health prior to domestic OP exposure lasting between one week and seven months, and all without other reported genotoxic exposures, were evaluated for chromosome aberrations and sister-chromatid exchange count per cell. Structural alterations in chromosomes were found in all of them; seven of eight subjects had chromosome aberrations outside the normal range for the laboratory, which was based on a control group of 141 subjects without known exposures and without illness; the eighth subject was reported to be "borderline." Sixty-three percent of subjects had slightly elevated levels of sister-chromatid exchanges.

A study of 61 male pesticide applicators in India (age 20 to 47) who worked in cotton fields without protective clothing were compared with a matched control group of 45 males (age 22 to 47) with no known pesticide exposure (Rupa et al., 1991). Pesticides included OPs such as malathion, methylparathion, monocrotophos, and quinalphos, as well as the pyrethroid cypermethrin and the OCs DDT and benzene hexachloride (BHC). The exposed group had a significantly higher frequency of sister-chromatid exchanges in peripheral lymphocytes than the controls (at each of three levels of exposure), with a monotonic dose-response relationship with exposure, and also showed cell cycle delay and decrease in mitotic index. For those in the highest exposure group (>20 years), the mean sister-chromatid exchanges per cell (±SD) compared with those of the controls were 10.54 ± 1.81 vs. 3.57 ± 1.85; and for the total exposed sample, the frequency was 8.46 ± 2.85 ($p < 0.05$) for each. However, because non-AChE-inhibiting pesticides were included in this analysis, it is not possible to conclude that OPs or AChE-inhibiting agents contributed to this effect.

Another study similarly examined sister-chromatid exchanges in peripheral blood lymphocytes in Italian flower-industry workers exposed to mixed pesticides (De Ferrari et al., 1991). Exposures included but were not confined to OPs; also included were exposures to nitro-organic herbicides and fungicides, hydrocarbon derivative herbicides, and inorganic fungicides and insecticides. The sample consisted of 32 healthy flower-industry workers, 32 individuals exposed to pesticides and hospitalized for bladder cancer, and 31 controls. A significant increase in chromosome aberrations and sister-chromatid exchanges was measured in lymphocytes of both exposed groups. Cancer patients had rare rearrangements (dicentrics, rings, and quadriradials) at a higher rate than healthy exposed persons; these were not observed in unexposed controls. Hyperdiploid and polyploid metaphases were also significantly increased in the two exposed groups. Stratifying for age and smoking did not change the substance of the results. Once again, the group exposed to mixed pesticides had higher rates of markers suggesting increased cancer potential; however, the contribution (if any) of OPs among the mix of exposures cannot be ascertained.

Finally, a study in Denmark compared 134 pesticide-exposed greenhouse sprayers with 157 referents (Landers and Rønne, 1995). Exposures among the sprayers included carbamates (the most widely used agents were benomyl—a carbamate fungicide—and pirimicarb), OPs, polychlorinated insecticides, pyrethroids, fungicides, and growth regulators. Sister-chromatid exchanges were higher among non-smoking but not among currently smoking sprayers than among matched referents. (Both age and smoking were related to significant increases in sister-chromatid exchanges, $p = 0.002$ and $p = 0.0005$, respectively). The frequency of pesticide applications, lifetime pesticide exposure, and in-season plasma-cholinesterase inhibition did not influence the sister-chromatid exchange frequency. Once again, it cannot be determined from these data whether AChE-inhibiting agents (carbamate or OP pesticides) contributed to the greater increase in frequency among non-smoking sprayers.

In Vitro Data Using Human Lymphocytes. A host of studies have examined mutagenic behavior of OPs and carbamates in human lymphocytes in vitro (Bianchi-Santamaria et al., 1997; Bonatti et al., 1994; Cid et al., 1990; Cid and Matos, 1984; Dolara et al., 1994; Garry et al., 1990; Lieberman et al., 1998; Lopez and Carrascal, 1987; Kappas et al., 1990; Kevekordes et al., 1996; Nicholas et al., 1979; Perocco and Fini, 1980; Veronesi and Ehrich, 1993; Rupa et al., 1991; Rupa et al., 1989; Rupa et al., 1988; Sobti et al., 1982). These studies examined a variety of OPs (including microtophos, malathion, chloracetophone, parathion, azinphos-methyl, dimethoate, pirimphos-methyl, diazinon) and carbamates (methomyl, aldicarb, propoxur, benomyl), as well as pesticide combinations, and reported interference in reparative DNA synthesis; increased damage to human lymphocyte DNA and interference with DNA repair processes after

damage exerted by ultraviolet rays; and OP-associated increases in mitotic index, sister-chromatid exchanges (Perocco and Fini, 1980), chromatid breaks, gaps, deletions, fragments, exchanges, dicentrics, and endoreduplications (Rupa et al., 1988). One study examined a variety of OP and carbamate compounds using a micronucleus test, with chemical doses based on subjects' estimated daily intake. Weak genotoxicity at these doses was seen in three of the four tested OPs and in the tested carbamate (benomyl); additive effects were not seen (Bianchi-Santamaria et al., 1997). The timing of exposure of the cell culture was also found to influence the susceptibility to chromosomal aberrations (tested with diazinon) (Lopez and Carrascal, 1987).

One study used a cell cloning assay to study genotoxicity of malathion to human T lymphocytes in vitro. Cells in phase G0 were exposed to doses of malathion ranging from 10 to 600 µg/ml (Pluth et al., 1996). In seven in vitro experiments using cells from four different individuals, and one experiment in an individual exposed in vivo, one or more independent mutants containing a partial deletion of exon 3 were isolated from each individual. In five of the seven mutants, the deleted regions overlapped extensively, indicating an area within exon 3 that is exceptionally prone to deletions upon exposure to malathion. It is uncertain what the molecular mechanism is, and how this could relate to agricultural workers' increased risk of cancer.

Neuroblastoma cell lines have also been examined (in humans and mice), and evidence suggests that interspecies selectivity in response to OP-related cytotoxicity is influenced by intercellular differences in metabolism and baseline esterase activity, as well as cytochrome-P450-associated monooxidase activity (Veronesi and Ehrich, 1993).

Studies in Microbial and Mammalian Systems. The possibility of carcinogenic effects is supported by in vitro studies demonstrating mutagenicity to bacteria, increased mammalian chromosomal damage and micronucleus formation, and sister-chromatid exchange, chromosomal aberrations, and transformation in cultured rat tracheal epithelial cells; DNA single-strand breaks in isolated rat hepatocytes; and increases in Syrian hamster embryo cell transformations and SA7 virus-induced transformations of hamster embryo cells, replicated in three different laboratories but requiring high doses of OPs in order to be cytotoxic (Mennear, 1998). Some reports suggest that the in vitro genotoxic effect may occur through direct alkylation, but in vivo metabolism of the parent molecule is thought to preclude this effect. Additional studies suggesting a genotoxic effect in mammals (usually with high dose exposures) and other studies failing to suggest such an effect have been reviewed (Mennear, 1998).

Many studies have examined the impact of OPs and carbamates on chromosomal aberrations, mutagenicity, and sister-chromatid exchanges in mammalian

systems, some with positive findings and some with negative findings (Chen et al., 1981; Degraeve and Moutschen, 1984; Degraeve et al., 1978; Dulout et al., 1982; Salvadori et al., 1988; Vaidya and Patankar, 1982; Wang et al., 1987). Although one report states that "most of the organochlorinated, organophosphorus, carbamate and pyrethroid group of pesticides were reported to be positive for cytogenetic effects in mammalian systems" (Rupa et al., 1989), evidence in cell cultures has not been wholly uniform. A study coauthored by the Dow Chemical company concluded that the OP chlorpyrifos has minimal mutagenic potential (Brenner et al., 1989). Another report concluded that "the genotoxic data to date have been somewhat inconclusive with regard to malathion exposure" (Pluth et al., 1996).

It has been suggested that some of the inconsistencies, particularly in the malathion data, may result from the difference between purified malathion (>99 percent pure) and technical-grade malathion, the grade used for agricultural purposes, which is usually 90 to 95 percent pure and may contain up to 11 impurities, some of which have been found to be significantly more toxic than malathion or to potentiate the toxicity of malathion (Pluth et al., 1996; Umetsu et al., 1977; Flessel et al., 1993). In addition, malaoxon, the active metabolite of malathion, tested positive for mammalian gene mutations in instances in which it was tested (Flessel et al., 1993). Adding to the inconsistency, most studies in bacteria and yeast have failed to show a mutagenic effect (Shirasu et al., 1975; Waters et al., 1982; Wong et al., 1989; Mohn, 1973; Wild, 1975), while studies in human lymphocyte cultures have commonly shown one (Pluth et al., 1996; Herath et al., 1989; Garry et al., 1990; Walter et al., 1980; Sobti et al., 1982; Nicholas et al., 1979). Rodent studies have been variable, depending on the assay (Degraeve et al., 1984; Degraeve and Moutschen, 1984).

The relationship between genetic effects and clinical disease is the subject of current investigations. While the presence of genetic effects is not always an indicator of clinical disease, these effects are important because of their association with increased cancer risk (Hagmar et al., 1994). Some evidence has suggested that low doses of some chemicals may be more genotoxic than high doses, so extrapolation from high to low doses may be misleading (Au et al., 1990).

Reproductive Effects

Data on whether OPs may produce adverse reproductive outcomes are presently unclear. Few studies that directly evaluate this issue are available in the literature. Many studies have assessed mutagenicity of OP and carbamate pesticides, which may relate to genotoxicity; and many of these studies have

suggested low-grade mutagenicity. However, there is little evidence of direct impact on reproductive outcomes.

Carcinogenic Effects

Data on both exposure and outcome are limited, and confounders remain important concerns, limiting the ability to draw epidemiological inferences. Available forms of data include

- Limited data from animal studies, compromised by known existence of interspecies differences.
- Studies of selected cancer rates in pest-control workers vs. referents, compromised by exposures to mixed pesticides and other potential confounders.
- Studies of cancer markers (in vivo) in pest-control workers' cells relative to controls, compromised by exposures to mixed pesticides.
- In vitro studies of cancer markers in human cells following exposure to specific pesticide agents, which permit identification of effects from OPs and carbamates dissociated from confounders, but are of less clear clinical relevance (in vitro data are reviewed in the section on genotoxicity).
- In vitro studies of cancer markers in animals (and microbes) following exposure to specific pesticide agents and combinations.

Carcinogenicity in Animal Studies. Debate continues concerning the possible carcinogenicity of some OPs in animals. An International Agency for Research on Cancer (IARC) monograph concluded that there was little evidence of strong mutagenic or carcinogenic effects in mammals from five commonly used OP pesticides (malathion, methyl parathion, parathion, tetrachlorvinphos, and trichlorfon) (International Agency for Research on Cancer, 1983), but interpretation of the underlying studies has been controversial (Minton and Murray, 1988; Huff et al., 1985; Reuber, 1981, 1985).

Among the potentially contradictory evidence are studies showing that dichlorvos causes a sex-specific, species-specific increase in a mononuclear cell leukemia: Male Fischer 344/N rats receiving up to 103 weeks of dichlorvos at either 4 mg/kg or 8 mg/kg by gavage experienced approximately twice as many cases of a mononuclear cell leukemia than those dosed only with the corn oil vehicle ($p = 0.012$ for 4 mg/kg; $p = 0.008$ for 8 mg/kg) (Mennear, 1998). No difference in rates was seen for female rats. The implications to humans of this sex- and species-specific increase are unclear. Moreover, the National Toxicology Program considered the results of the female mouse (but not the male

mouse) portion of study to afford unequivocal evidence of carcinogenesis (Mennear, 1994). It has been noted that dichlorvos "possesses no in vivo mutagenic activity in mammalian assay systems, and it bears no significant structural similarity to known carcinogens," so one author considered "a weight-of-the-evidence analysis" to lead to the conclusion that dichlorvos "poses neither mutagenic nor carcinogenic risks to humans exposed under normal conditions of use or foreseeable conditions of misuse" (Mennear, 1994).

Studies of Carcinogenicity in Humans. A number of epidemiological studies report a statistically significant increase in death from hematological malignancies among persons in farming occupations (Milham, 1971; Cantor, 1982; Blair et al., 1985; Hoar et al., 1986; Brown et al., 1990; Pasqualetti et al., 1991). It cannot be presumed that AChE-inhibiting OP and carbamate pesticides are necessarily responsible for these findings, but increased mutagenicity and genotoxicity of OP and carbamate agents to human lymphocytes in vitro (data reviewed previously) take on new significance in light of these reports.

Leukemia and Lymphoma. Data regarding whether OP pesticides are risk factors for leukemia remain inconclusive. Many studies have demonstrated an apparent increased risk of lymphoma and leukemia in farmers (Brown et al., 1990), and some have shown an apparent increased odds ratio (OR), or crude odds ratio, for leukemia (Brown et al., 1990) and lymphoma (Persson et al., 1993). Although in some cases the significance of the effect is lost following adjustment for other factors (Persson et al., 1993), it is difficult to know whether those factors might be merely correlated with pesticide use rather than causal in a fashion that causes adjustment to "adjust out" a true effect. In a population-based case-control study in Iowa and Minnesota of 578 white men with leukemia and 1,245 controls, "significantly elevated risks for leukemia of ≥2.0" were seen for exposure to the OPs crotoxyphos (OR = 11.1), dichlorvos (OR = 2.0), and lamphur (OR = 2.2), as well as the natural product pyrethrins (OR = 3.7) and the chlorinated hydrocarbon methoxychlor (OR = 2.2) (Brown et al., 1990). Clearly, additional research is warranted to assess the relationship between leukemia and lymphoma and OP (and perhaps carbamate) exposure.

Non-Hodgkin's Lymphoma. Some studies suggest a relationship between pesticides, including OPs and carbamates, and non-Hodgkin's lymphoma (NHL), a tumor whose incidence rates have increased worldwide in both men and women for 30 years (Milham, 1971; Cantor, 1982; Blair et al., 1985; Hoar et al., 1986; Brown et al., 1990; Pasqualetti et al., 1991).

Lung Cancer. Some studies of male pest-control workers have reported an increased risk of lung cancer linked to the number of years subjects have been licensed. One study reported a standardized mortality ratio (SMR) of 1.4 from

lung cancer in pest-control workers in Florida, rising to 2.9 among workers employed for more than 20 years (Blair et al., 1983). This study was limited by lack of information on smoking status and on specific pesticides. In an effort to redress these defects, a nested case-control study was performed to determine the relation of smoking and type of pesticide to risk, comparing 65 deceased lung cancer cases, 122 deceased controls, and 172 living controls, using information obtained from interviews with next of kin for both living and dead subjects. ORs for lung cancer were 2.4 (95 percent CI = 1.0–5.9) for deceased controls and for workers first licensed before age 40, and increased from 1.4 (95 percent CI = 0.7–3.0) for those licensed 10 to 19 years to 2.1 (95 percent CI = 0.8–5.5) for those licensed 20 or more years. The risk of cancer was greater among pest-control operators than among non–pest-control operators. (The increase in risk was not significant among the living controls: OR = 1.5, 95 percent CI = 0.6–3.3.) Although small, the lung cancer risk among pest-control operators appeared to be possibly associated with reported exposure to carbamates (OR = 16.3, 95 percent CI = 2.2–122.5, dead controls), OPs (OR = 2.2, 95 percent CI = 0.8–5.5, dead controls), and phenoxyacetic acids (OR = 4.8, 95 percent CI = 0.6–35.5, dead controls); and to the specific OP diazinon (OR = 2.0, 95 percent CI = 0.7–5.5, dead controls) and the specific carbamates carbaryl (OR = 4.2, 95 percent CI = 0.6–27.2, live controls; data not given for dead controls) and propoxur (OR = 12.4, 95 percent CI = 1.5–100.3, dead controls; OR = 1.4, 95 percent CI = 0.4–5.5, live controls). OR estimates were lower when living controls were used, except in the case of phenoxyacetic acids. Compared with the general U.S. mortality experience, overall mortality was not elevated, although lung-cancer-specific mortality was increased.

POTENTIAL HEALTH EFFECTS OF CARBAMATES

Carbamates have the same presumed primary mechanism of toxicity as OPs; that is, they are both AChE inhibitors. Thus, even though OPs inhibit AChE irreversibly (requiring more enzyme to be produced for function to be restored), whereas carbamates inhibit AChE reversibly, OPs and carbamates are often considered together (Lerman et al., 1984; D'Mello and Sidell, 1991; Bardin et al., 1994). The literature regarding the acute and chronic effects of carbamates has largely been reviewed in the previous sections.

There are two major classes of pesticidal carbamates (Miller 1982). The first class is ChE-inhibiting carbamates, including monomethylcarbamates and dimethylcarbamates. These are used primarily as insecticides (both contact and systemic) and also as miticides, rodenticides, nematocides, anthelmintics, and molluscides; in addition, they are used for treatment of glaucoma and myasthenia gravis, and as antagonists for curare or curarimimetic poisoning

(Miller, 1982). The methylcarbamates and dimethylcarbamates inhibit ChE by carbamylation of the esteratic site of the enzyme; and in the case of AChE, they prevent the enzyme from de-esterifying ACh. Some selectively inhibit either "true" cholinesterase (RBC AChE or simply AChE, found in red blood cells and nervous tissue) or butyrylcholinesterase (BuChE, or psuedocholinesterase or plasma cholinesterase) or both; others selectively inhibit peripheral ChEs (Miller, 1982). Cholinesterase-inhibiting carbamates are often referred to as "reversible ChE inhibitors," although this designation has been criticized on the grounds that it suggests that they dissociate from the enzyme intact, whereas they are covalently bound to the active site of the enzyme and are typically hydrolyzed in the same manner as is acetylcholine (Miller, 1982, citing 39, 57). These carbamates can be biotransformed through any of several metabolic mechanisms, including N-demethylation, aromatic ring hydroxylation, O-dealkylation, alkyl hydroxylation, and sulfoxidation; however, hydrolysis of the carbamate moiety is the major route of metabolism. In instances in which biotransformation does not involve separation of this ester bond, the metabolic products may also be ChE inhibitors and may be more potent than the parent compound (Miller, 1982).

The other major class is the dithiocarbamates, sulfur-containing carbamates which may have little or no esterase-inhibiting action and which are often, but not exclusively, used as fungicides and herbicides. These include methyldithiocarbamates, dimethyldithiocarbamates, diethyldithiocarbamates, and ethylenebisdithiocarbamates. These are highly reactive due to their metal-combining capacity and their ability to interact with sulfhydryl-containing compounds. The pesticides of concern identified by OSAGWI do not include dithiocarbamates, and this class is not discussed further in this report.

Hepatitis has been reported to have followed exposure to carbamates, specifically pyricarbate (pyridinol carbamate) (See and Bouvry, 1984; Grange et al., 1984). Carbamates are not known to produce OPIDN or intermediate syndrome in the absence of OPs; they may, however, cause these syndromes to occur when they otherwise might not if carbamate exposure occurs after exposure to an OP that may cause OPIDN or intermediate syndrome.

Genetic Effects

Information on genetic effects of carbamates was reviewed in the previous section, where some cited studies evaluated both OP and carbamate agents.

As stated previously, "most of the organochlorinated, organophosphorus, carbamate and pyrethroid group of pesticides were reported to be positive for cy-

togenetic effects in mammalian systems" (Rupa et al., 1989), although findings are not consistent.

Studies have included carbamates (e.g., methomyl, aldicarb, propoxur, benomyl) as well as pesticide combinations. One study examined a variety of OP and carbamate compounds using a micronucleus test, with chemical doses based on subjects' estimated daily intake. It found weak genotoxicity at these doses for three of the four tested OPs and for the tested carbamate (benomyl) (Bianchi-Santamaria et al., 1997).

Reproductive Effects

Little independent information on the reproductive effects of carbamates was reviewed. High dose rates of the carbamate fungicide benomyl have been linked to eye defects (including anophthalmia) in humans and to reproductive effects in animals (Handysides, 1993; Watterson, 1994), but these findings do not appear to extend to other carbamates.

Carcinogenic Effects

Few data directly relating carbamate exposure to cancer in humans have been reported.

In a nested case-control study (described above) that compared 65 deceased lung-cancer cases, 122 deceased controls, and 172 living controls, using information obtained from interviews with next of kin for both living and dead subjects, lung cancer risk among pest-control operators appeared to be possibly associated with reported exposure to carbamates (OR = 16.3, 95 percent CI = 2.2–122.5, dead controls) and to the specific carbamates carbaryl (OR = 4.2, 95 percent CI = 0.6–27.2, live controls; data not given for dead controls) and propoxur (OR = 12.4, 95 percent CI = 1.5–100.3, dead controls; OR = 1.4, 95 percent CI = 0.4–5.5, live controls). OR estimates were lower when living controls were used. Compared with the general U.S. mortality experience, overall mortality was not elevated, although lung-cancer-specific mortality was increased.

Additional data relating cancer to carbamate exposure, as part of pesticide exposure more generally, are reviewed in the section discussing OPs and cancer.

Data pertaining to genetic effects of carbamates, which may pertain to cancer risk insofar as mutagenicity relates to carcinogenicity, are presented in the section on OPs and genetic effects, where some of the reviewed studies describe effects of carbamates as well as OPs. Carbamates have been shown to have genetic effects similar in character to those observed with OPs.

SYNTHESIS

Symptoms found to occur following exposure to AChE inhibitors such as OP and carbamate pesticides include fatigue, joint and muscle symptoms, sleep effects, headaches, skin effects, cognitive effects, mood effects, and neurological effects. These classes of symptoms are also seen frequently in ill PGWV—they are among the most frequent principal diagnoses in the PGW registry (see Chapter Three). This observed similarity in symptoms of ill PGWV and persons exposed to AChE inhibitors is not sufficient in itself to conclude that OP and carbamate pesticide exposure is a cause of the myriad health problems reported by PGWV. However, we believe it is inappropriate at this point to conclude that such exposures played no role. In the absence of better information about such exposures, the similarity in symptoms is sufficient to consider pesticide exposures among the potential causes of undiagnosed illnesses in PGWV that cannot be eliminated on the basis of a review of published evidence to date.

Comparatively few studies directly assess the impact of *short-term* AChE-inhibitor exposure, without acute toxicity, on *long-term* symptoms and neuropsychological and neurobehavioral outcomes. However, there is evidence of modest long-term effects on these outcomes following AChE-inhibitor exposures that were insufficient to lead to acute symptoms or medical attention, and there is tentative evidence to suggest that these findings may occur selectively in persons who experience more-pronounced symptoms on acute exposure (Beach et al., 1996). There is also evidence of modest long-term effects on cognitive outcomes in ill PGWV.

Additional comprehensive evaluations of larger samples of subjects previously exposed to OP and carbamate pesticides, including those who did and did not experience symptoms on acute exposure and others whose period of exposure was short, would be useful in predicting possible specific effects in ill PGWV if AChE-inhibitor exposures are found to be a contributor to undiagnosed illnesses among this population.

Chapter Eight

CONFOUNDING FACTORS: INDIVIDUAL DIFFERENCES AND INTERACTIONS

INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY TO PESTICIDES

This chapter presents and discusses some of the circumstances and conditions that may confer differing susceptibilities on different individuals and populations. Differences at the basic individual level, i.e., genetic differences, are an important source of differences in susceptibility. For example, as discussed in Chapter Four, DEET is especially toxic to individuals with genetic or acquired defects in ammonia metabolism such as carriers of ornithine carbamoyl transferase (OCT) deficiency. In addition to genetic differences, heterogeneity in human populations may be expected to produce differences in susceptibility. However, even homogeneous populations of test animals often display a distribution of effects in response to toxic challenge, which indicates that other individual differences must also be important. These may include differences in exposure, absorption, and resulting effective doses.

Exposure and Absorption Differences

Many factors may affect the rate and magnitude of pesticide absorption. Mode of delivery, of course, affects the primary route of absorption (e.g., dermal or ocular absorption, inhalation), and for each route, individual factors condition the amount absorbed in "comparable" exposures. Protective clothing and individual differences in skin properties and integrity influence dermal exposure (Aprea et al., 1994; Keeble et al., 1993; Kishi et al., 1995; Lander and Hinke, 1992). Inhalational exposure may vary with ventilation and may also be affected by other factors, including properties of airway membranes. Intestinal absorption may be highly variable and is itself in turn affected to varying degrees by AChE-inhibitor exposures themselves (and consequent increased peristalsis). Moreover, the actual position of the individual with respect to the source of the exposure (for inhalational exposure) and differences in handling

(for dermal exposure) may lead to widespread differences in de facto exposure levels among individuals in the same "setting."

Clearance Differences

Differences in clearance of pesticides depend on the amounts, genotype, and activity of enzymes involved in their metabolism. For example, mammals are protected from OPs by at least two mechanisms: First, BuChE binds these agents, sequestering them from neural tissue; second, paroxonase/arylesterase metabolizes OPs by hydrolysis, rendering them harmless products that are excreted (Haley et al., 1999a; Mutch et al., 1992; Li et al., 1993, 1995; Shih et al., 1998).

There are widespread differences in the genetics and activity of these enzymes from one individual to another. For example, Golomb (1999) noted that genetic polymorphisms in BuChE could have a role in differing clearance rates. The K-variant of BuChE and, more rarely, atypical BuChE lead to reduced clearance rates. There are also differences in the activity of enzymes even when the same genotype is present; moreover, these differences may themselves depend to some degree on prior exposures.

Clearance differences were shown to be important in a study of 1,003 workers exposed to the alkyl phosphate OPs methylparathion (n = 135) and ethyl-parathion (n = 169), the carbamate propoxur (n = 233), the pyrethroid cyfluthrin (n = 440), methyl-parathion and cyfluthrin (n = 19), or propoxur and cyfluthrin (n = 7) (Leng and Lewalter, 1999). Plasma levels, urine metabolite levels, and activity of plasma ChE and AChE were measured. At the same propoxur plasma concentration, only subjects with low individual AChE activity reported symptoms. Wide variation was present in baseline (pre-employment) AChE levels, with 100 workers having pre-employment ACh activity below the range of the published reference values (2,900 to 4,100 units per liter (U/l)). Inhibition values, ranging from 17 percent to 64 percent in 135 workers exposed to propoxur after an accident, were related to pre-exposure values. Symptoms of tearing, sweating, fatigue, dizziness, and visual disturbances were seen primarily in subjects with baseline AChE activity below 3,000 U/l (Leng and Lewalter, 1999). Among 10 workers who reported symptoms following exposure to cyfluthrin alone or in combination with other agents, the cyfluthrin plasma half-life ranged from 1.5 hours to 14 hours, more than a ninefold range.

In contrast, subjects who metabolized cyfluthrin rapidly reported fewer symptoms than those with a lower rate of metabolism, a tendency also evident with mixed exposure (cyfluthrin and methylparathion) (Leng and Lewalter, 1999), indicating the importance of individual susceptibility in determining the potential for toxic effects.

Paraoxonase. Paraoxonase (PON or PON1) is a high-density lipoprotein-bound "A-esterase" that is active in metabolizing (via hydrolysis) OPs to varying degrees. For example, it is more active toward chlorpyrifos oxon than paraoxon (Sultatos et al., 1984, 1985; Costa et al., 1990; Li et al., 1993 in Richardson, 1995). It is not thought to play a direct role in metabolism of pyridostigmine bromide (PB) (Furlong et al., 1989), nor does the literature contain information indicating a role in the breakdown of other carbamates.

Paraoxonase is an important factor determining the toxicity of OP pesticides and nerve agents to mammals, presumably including humans (Costa et al., 1990, 1997; Li et al., 1993, 1995; Davies et al., 1996). There are two polymorphic sites at amino acid positions 55 (L → M) and 192 (G → A). The Gln192 form is classically defined as the "A" or "Q" genotype, while the Arg192 is known as the "B" or "R" genotype (Haley et al., 1999; Mackness et al., 1996, 1997). A study of the influence of these polymorphisms on PON activity in 279 healthy human subjects (Mackness et al., 1997) showed that the 55 polymorphism significantly affected PON activity, with the MM homozygotes demonstrating more than 50 percent less activity toward paraoxon than the LL and LM genotypes, irrespective of the 192 genotype (Mackness et al., 1997). Previous studies had already shown that 192 polymorphism had an impact on PON activity. Multiple regression showed that the 192 polymorphism, 55 polymorphism, and serum PON concentration were responsible for 46, 16, and 13 percent of the variation in PON activity, respectively (all $p < 0.001$); no other examined parameters influenced PON activity. This suggests that AA/MM and AB/MM individuals may be more susceptible to OP intoxication; however, between the A and B genotypes, the type that is better at hydrolyzing paraoxon (Type A) is less adept at hydrolyzing sarin (as well as diazinon and soman) (Davies et al., 1996), so susceptibility depends on the OP to which one has been exposed. For additional discussion of PON, see Golomb (1999).

Chlorpyrifos Oxonase. Chlorpyrifos oxonase is an important metabolizing enzyme for certain OPs (such as chlorpyrifos). Individual differences in hydrolyzing efficacy appear to result from differences in activity but not from genetic differences. Following hydrolytic cleavage of chlorpyrifos oxon by chlorpyrifos oxonase to products that are much more water soluble, the OP is eliminated relatively rapidly from species ranging from fish to rats and humans and is considered to have a substantially lower potential to accumulate with repeated exposures at relatively low doses (Richardson, 1995; Eto, 1979; Nolan et al., 1984.; Sunaga et al., 1989; Barron et al., 1991). Brain AChE inhibition in rats dosed with chlorpyrifos oxon is greatly reduced by prior IV injection of paraoxonase (Costa et al., 1990; Richardson, 1995), suggesting the important reduction in toxicity conferred by this enzyme.

Differences across species in the activity of chlorpyrifos oxonase vary with LD_{50}s for chlorpyrifos. Rabbits have 40 times greater chlorpyrifos oxonase activity than do rats, and about sevenfold to twentyfold higher LD_{50}s of chlorpyrifos (rabbit LD_{50} is 2,000 mg/kg, per os [p.o.] in corn oil; rat LD_{50} is 118 to 245 mg/kg p.o. in corn oil) (McCollister et al., 1974; Richardson, 1995); and low LD_{50}s for chlorpyrifos in hens (50 mg/kg p.o. in gelatin capsules) (Rowe et al., 1978; Richardson, 1995) are thought to reflect the very low levels of serum A-esterases generally present in bird species (Brealy et al., 1980; Costa et al., 1990).

In contrast to the results for paraoxon, human chlorpyrifos oxonase activity has not been shown to have clear genetic polymorphism, but a four- to fivefold (Furlong et al., 1988) or even a thirteenfold variation in chlorpyrifos oxonase activity has been found in human serum (Richardson, 1995). Chlorpyrifos oxonase is among the enzymes for which individual differences may influence susceptibility to effects of selected pesticides; in this case, the differences are in activity and are not genetic.

Differences in Metabolizing Enzymes Among PGWV

Some studies have shown no significant differences in atypical BuChE between PGWV who have entered registries and those who have not (see Golomb, 1999). However, this very rare polymorphism alone could not readily account for large differences in illness, so this finding is not wholly unexpected. Golomb (1999) suggested that more common polymorphisms, such as paraoxonase and the K-variant of BuChE, receive increased attention and that enzyme activity, not just genetic type, should be examined.

One study found that ill PGWV with neurological symptoms had 3.5 times higher odds of having the R allele of paraoxonase (either QR or RR, vs. the QQ genetic composition) than did healthy controls (95 percent CI = 1.01–12.18, $p < 0.05$) (Haley et al., 1999a). Moreover, low activity of the Q alloenzyme (the alloenzyme that is more efficient at hydrolyzing several OPs, including diazinon, as well as sarin and soman) (Haley et al., 1999b) distinguished ill PGWV from controls, and did so more accurately than the PON1 genotype or the activity levels of the type R alloenzyme, total arylesterase, total paraoxonase, or BuChE. The OR of being in the lowest quartile of Type Q arylesterase activity in ill PGWV compared with controls was 4.5 (95 percent CI = 1.24–16.35, $p = 0.02$), and for those with the comparatively severe symptom complex 2, the OR was 9.0 (95 percent CI = 1.72–46.99) compared with controls. There was a trend toward ill PGWV having lower BuChE activity; the OR for being in the lowest quartile for BuChE activity was 2.67 for all veterans, but this did not reach significance ($p = 0.2$, 95 percent CI = 0.6–11.8). This trend merits evaluation in a larger sample.

Low activity of the Q alloenzyme was also associated with acute toxicity after taking PB (although paraoxonase is not believed to break PB down), and acute symptoms in response to PB had previously been linked to development of either of two of the three main factor-analysis-derived syndromes in PGWV identified by Haley et al. (1999b). The study of paraoxonase alloenzymes was conducted on a sample of 25 ill PGWV meeting criteria for Haley's symptom complex 1 (n = 5), 2 (n = 12), or 3 (n = 5), and one each with symptom complexes 4 to 6; the controls were 20 healthy veterans matched for age, education, and sex. Mean type Q activity was significantly lower in men at or over 45 years of age than in younger men ($p = 0.009$). There also was a possible trend toward ill PGWV having lower BuChE levels (most of those at the lowest levels were ill rather than healthy), although the allelic variant was not associated with illness in this study.

Nutritional and Other Cofactors

Individual differences in cofactors that modify the effect of pesticides, are essential for metabolism of pesticides, or permit or inhibit toxic effects by pesticides may contribute to individual differences in clinical effects. These differences may depend on exogenously introduced factors (such as antioxidant vitamins C and E, phytochemicals, and cholesterol) and could thus be construed as interaction effects. Vitamins E and C may confer protection not only against OPs and carbamates (Grabarczyk and Kopec-Szlezak, 1992; Khan and Sinha, 1996), but also against other pesticides, such as organichlorines (OCs) (Podstawka et al., 1991) and pyrethroids (Flannigan et al., 1985; Tucker et al., 1984), with which OPs and carbamates may interact.

INTERACTIONS

General Issues

Exposures to pesticides in combination with other agents may exert effects different from those experienced with pesticides alone. Moreover, effects from two pesticides may differ from those expected from each separately. Therefore, this review includes the literature that considers pesticides in combination with other exposures.[1]

[1]In this section, we explore various other exposures, including heat, dietary factors, and illegal drugs. This is not to suggest that these exposures were known to occur with specific frequency during ODS/DS; rather, the discussion is intended to summarize some of what is known about the interaction of these and other exposures with pesticides. A forthcoming report being prepared by OSAGWI, *Pesticides Environmental Exposure Report* (OSAGWI, 2000), investigates pesticide exposures during ODS/DS and draws conclusions based on all the available evidence.

It is not feasible to predict the toxicity of agent mixtures in general, or of pesticide mixtures (or pesticides in combination with other agents) in particular, on the basis of the toxicity of single compounds (Marinovich et al., 1996). Moreover, the number of possible combinations increases exponentially with the number of agents, as 2^n; thus, 10 compounds have over 1,000 possible combinations that could have different consequences. When agents are experienced together, the effect may be additive, synergistic, or antagonistic, and the character of the interaction may differ for different effects of the compounds. Because of the computational intractability of studying every possible combination, the FDA does not require examination of drug combinations in determining approval for an individual drug; it does not even require examination of combinations that may commonly occur together. Similarly, health consequences of pesticide mixtures, and coexposures to pesticides and other factors, are in general poorly understood, and "testing even most potential mixtures with the classical toxicological protocol is unfeasible" (Marinovich et al., 1996). However, it is conceivable that multiple exposures to pesticides and other compounds occurred during ODS/DS, underscoring the need for further investigation to focus further research. Some of the possible multiple exposures encountered during ODS/DS are discussed below.

Interactions Among DEET, PB, and Pesticides

The Institute of Medicine (IOM, 1996) and the National Research Council (NRC, 1994) have stated that studies are needed to resolve uncertainties about the effects of DEET, PB, and other pesticides in combination. Some studies have been conducted in response to questions raised after the Gulf War concerning whether the combinations of these exposures might be related to health complaints of veterans.

Some data are available concerning mixtures of pesticides with the insect repellent DEET. Because DEET may enhance the dermal penetration of other chemicals and because of its ubiquitous use, several studies have focused on the combination of exposures PGWV may have encountered during ODS/DS. For example, PGWV could have applied DEET and permethrin as prescribed by the DoD Insect Repellent System (Young and Evans, 1998) and at the same time taken PB tablets as a prophylactic treatment for nerve agents.

In two studies by Abou-Donia et al. (1996a,b), adult hens exposed to the combination of DEET, PB, and either permethrin or chlorpyrifos showed greater-than-additive (not synergistic) effects when exposed to two of the three compounds, and there was an even greater effect when all three chemicals were present. The authors suggest that this could mean that agents such as PB,

which ordinarily do not reach the brain, can enhance the neurotoxicity of chlorpyrifos, which is known to do so. Similarly, while DEET does not exhibit cholinergic effects, it may enhance this effect from other chemicals. The authors hypothesize that three mechanisms could be responsible for the interactive effects. First, concurrent exposure to these chemicals may enhance their absorption. Second, the chemicals may be competing substrates, resulting in a decreased catabolism of the combination of chemicals. Because such competition could increase the likelihood that these chemicals are transported to nerve tissue, individual variations in plasma and liver esterases would highlight subpopulations that are more susceptible to neurotoxins. Third, the concurrent exposure to all three chemicals could cause trauma to the cerebrovasculature, thereby increasing vascular permeability or altered blood flow to the brain.

It should be noted, however, that both DEET and permethrin were administered in these studies at high doses (500 mg/kg), and the route of exposure, subcutaneous injection, may limit the relevance of the findings. The exposure values used in this study would be equivalent to a 70-kg person being exposed to 467 tablets of PB, 1,667 cans of permethrin, and 76 tubes of 33 percent DEET. The implications of these studies are unclear when trying to understand the potential for human health effects at lower doses; however, the inference that mixtures can lead to effects exceeding or distinct from the component parts deserves further attention in the context of Gulf War illnesses.

McCain et al. (1997) evaluated the lethal interaction of DEET, PB, and permethrin when given orally to rats by gastric gavage. A significant increase in lethality over expected additive values occurred when all three chemicals were given concurrently. This study also used high doses of these chemicals, sufficient for a single dose to produce a lethal effect. They calculated that to match the lowest doses used in their study (PB = 46 mg/kg, permethrin = 279 mg/kg, DEET = 1,946 mg/kg), a 70-kg person would have to simultaneously ingest 107 PB tablets, 23 cans of permethrin, and 6.6 tubes of 33 percent DEET. As in other such studies, the method of DEET and permethrin exposure (ingestion) also presents difficulties in applying these findings to an understanding of health effects in humans. Baynes et al. (1997) make this point and hypothesize that the exposure route strongly affects the bioavailability of these chemicals, suggesting that significantly less DEET and permethrin would be bioavailable following dermal exposure than following oral or subcutaneous exposure. In their study, no permethrin was absorbed in the skin of either rats, mice, or pigs when it was applied topically with DEET at either 15 or 35 percent concentration and using a number of different solvent mixtures. In fact, DEET appeared to decrease permethrin absorption in mouse skin, which is more permeable than human skin. In addition, the exposures in this study were limited to eight hours, which may limit the applicability of the findings to any Gulf War exposure scenario.

Clearly, longer-term absorption studies are warranted before conclusions regarding the interaction between DEET and other chemicals (especially pesticides) can be drawn. Also, it should be considered that the estimated area of overlapping between DEET-treated skin and permethrin-treated uniforms is small—approximately 5 percent or less—and therefore is probably of little importance in view of the limited amounts of dual exposures (NRC, 1994).

Interactions Among Pyrethroids, Organophosphates, and Carbamates

Pyrethroids have a number of proposed mechanisms of toxicity, chief among which are reduction in Na+K+-ATPase (which has been documented in mammalian studies in various brain regions, including frontal cortex, hippocampus, and cerebellum) (Husain et al., 1996) and increase in monoamine oxidase activity leading to shifts in polyamines (Husain et al., 1994). Although pyrethroids are not normally thought to exert their effect primarily through AChE inhibition, they have been reported to influence ACh activity by

- Increasing AChE not only in blood and bronchoalveolar lavage fluid (Jian and Tian, 1996), but also in brain regions, including the frontal cortex, striatum (basal ganglia), hippocampus, cerebellum, and pons medulla in mammalian studies (Husain et al., 1996).
- Affecting ACh concentrations in the brain (Aldridge et al., 1978).
- Increasing striatal muscarinic receptors and altering nicotinic receptors (Eriksson and Nordberg, 1990; Eriksson and Fredricksson, 1991; Husain et al., 1996).

Effects through the ACh system constitute one mechanism by which interactions of pyrethroids with OP and carbamate pesticides may be mediated, although many other mechanisms of interaction are possible. (For example, it has been suggested that changes in the physiological concentration of polyamines may produce effects on cholinergic and dopaminergic systems by adversely affecting calcium homeostasis, experience-dependent brain growth, and neurotransmitter uptake, thus leading to derangements in overall synaptic events (Husain et al., 1994).

It should be noted that persistence of pyrethroids in the fat and brain of exposed subjects has been reported in animal studies and in studies of poisoned cotton sprayers (Husain et al., 1996), so the possibility of interactions occurring even with a delay following pyrethroid exposure remains a concern.

Pesticide Formulations

As has been noted, the active ingredient on a pesticide label relates only to activity against the species targeted by the substance. However, many of the inactive ingredients in pesticide formulations (e.g., the petroleum distillates) can also have harmful effects on humans. In most cases of observed human effects of pesticide exposure, the exposure was to a pesticide formulation; however, in many animal or other laboratory studies, only the active ingredient is tested. It is possible that not only might inactive ingredients of pesticide formulations pose a hazard to human health, these ingredients may act in combination with the active ingredient to produce an effect different from that predicted from animal models.

Pesticide Interactions with Drugs and Other Exposures

The IOM issued a report on interactions among drugs and chemicals and proposed a mechanism for evaluating whether presumptive interactions were likely (Committee to Study the Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces, 1996). The thesis of the report was that if there were similar loci of effect, interactions would be more likely to occur, and concern regarding interactions should be heightened. Although this approach is on its face sensible, it has several limitations (Golomb, 1999). For example, while PB was represented as having effects (and therefore potential interactions) only on the nervous system, in fact PB has documented effects on virtually all of the systems listed. Therefore, use of this approach does little to restrict the domains of consideration, or the exposures with which PB might interact, provided a sufficiently comprehensive examination of the evidence is employed to determine loci of effect.

The report on PB characterizes interactions between it and heat, stress, caffeine, nicotine, and antihistamines. Because other carbamates, as well as OPs, share with PB the major pharmacological effect of AChE inhibition, the data on potential interactions with these agents also have bearing here.

Pyridostigmine Bromide. One hypothesis is that primarily peripheral binding of AChE by PB will occupy peripheral binding sites and potentially drive a higher fraction of OP pesticides to central binding sites. Thus, a synergistic effect on central ACh regulation may ensue.

Heat. In addition to its possible impact on the blood brain barrier, heat affects acetylcholinergic nerve terminal function. The effects of heating and cooling on electrophysiological testing and acetylcholinergic function are complex and have long been studied (Adrian, 1914; Delbeke et al., 1978; Denys, 1991; Gasser, 1931; Hofmann et al., 1966; Lang and Pusa, 1980; Lass and Fischback, 1976;

Lowitzsch et al., 1977; Rutchik amd Rutkove, 1998; Rutkove et al., 1997; Stegeman and Weerd, 1982; Tasaki, 1949). Cooling prolongs the refractory period of nerve and muscle, increases facilitation, decreases AChE activity, decreases the amount of ACh released, and increases the amplitude of the excitatory endplate potential (Rutchik and Rutkove, 1998). Insofar as heat may produce effects tending in the opposite direction, it may be linked to comparatively increased amounts of ACh released, potentially exacerbating the effect of AChE inhibitors (although the net impact of this and changes in AChE activity are difficult to ascertain). Heating is associated with reductions in the amplitude of spontaneous repetitive motor action potentials with OP poisoning (analogous to the finding seen in patients with myasthenia gravis) (Rutchik and Rutkove, 1998).

The net impact of any of these effects on the clinical impact of AChE-inhibitor exposure is not well defined, although heat has been reported to exacerbate the effect of AChE-inhibitor exposures (Richter et al., 1992). For instance, depression in ChE activity has been found to be increased with heat stress and dehydration (Baetjer, 1983), and heat stress and heat strain were found to be hazards for pesticide-spray pilots (Gribetz et al., 1980; Richter et al., 1992). Not only may heat modify the impact of AChE-inhibitor exposure, AChE inhibitors may conceivably modify the impact of heat by increasing body temperature. In a study of 70 cases of acute carbamate and OP poisoning in Jordan (where 58 percent of the subjects were intoxicated with carbamates), 47 percent had low-grade fever (37.5°C to 38.5°C) with no evidence of infection, and all resolved spontaneously within five days (Saadeh et al., 1996). However, the report does not discuss whether lower doses produce an effect on body temperature.

An additional concern is that increased body temperature (e.g., to 39°C) is associated with increased ischemia-induced blood brain barrier permeability. Cooling attenuates post-ischemic blood brain barrier consequences and the rise in extracellular glutamate that accompanies this attenuation (Dietrich et al., 1992).

Antihistamines. Some AChE inhibitors have been shown to influence histamine function. For example, malathion metabolites cause rapid release of histamine from basophilic cells, and with prolonged incubation malathion itself does, suggesting that these cells may metabolize malathion (Xiong and Rodgers, 1997).

Antihistamines also have potential cholinergic effects. Histamine modulates heat-stress-induced increases in blood brain barrier permeability, which may be enhanced by histamine H1 receptor blockers and reduced by histamine H2 receptor blockers (Sharma et al., 1992). Histamine H2 receptor blockers have been shown to have AChE-inhibiting effects that are stronger for ranitidine and

nizatidine than for cimetidine (Laine-Cessac et al., 1993). Moreover, histamine H1 blockers have been shown to increase central ACh and ACh action in animal studies (Dringenberg and DeSouza-Silva, 1998). Thus, H1 blockers at the time of OP or carbamate exposure might worsen effects by heightening brain penetration and augmenting the excess of ACh available centrally. The possible treatment impact of antihistamines in ill PGWV or post-AChE-inhibitor-exposure subjects remains to be determined.

Because antihistamines have effects on cholinergic function, and AChE inhibitors have effects on histamine, interactions between antihistamines and OP/carbamate pesticide exposure might be anticipated.

Diet, Alcohol, and Dietary Supplements. Studies in rats have demonstrated that diet can affect susceptibility to the adverse effects of pesticides, including inhibition of serum aliesterase and AChE activity in liver microsomes. Rats on low-protein diets were found to be more markedly affected by pesticide exposure, both acute and chronic OP, as well as OC (Casterline and Williams, 1969, 1971; Baron et al., 1964; Baron et al., 1966; Boyd, 1969; Lee et al., 1964; Weatherholtz et al., 1969).

Possible mechanisms of interaction among pesticides that are related to diet and alcohol intake include membrane effects. Some classes of pesticides, including pyrethroids (Moya-Quiles et al., 1995), OCs (Suwalsky et al., 1997a,b; Verma and Singhal, 1991; Antunes-Madeira et al., 1993) and perhaps DEET, may also have membrane effects including fluidization of membranes. The OP pesticides influence and may fluidize membranes (Wysocki et al., 1987), which in turn affects membrane function, including neurotransmitter receptor expression, and the effect is aggravated by low cholesterol. Moreover, dietary fatty acid composition also appears to influence membrane fluidity and function (Block and Edwards, 1987; Clandinin et al., 1991; Clandinin et al., 1982; Gould and Ginsberg, 1985; Greenwood et al., 1989; Heron et al., 1980; Johnson et al., 1979; Scott et al., 1989; Shinitzky and Inbar, 1974). Thus, dietary fat composition may interact with pesticides in exacerbating membrane fluidization.

Alcohol also fluidizes membranes (Johnson et al., 1979) and cannot be excluded as an exacerbating factor. Studies have shown antioxidant vitamins to have protective effects on lipid peroxidation and oxidative damage, which OP agents have been shown to cause (Barja et al., 1994); however, it should be noted that the dose of vitamin may determine whether it has primarily an oxidant or an antioxidant effect. In addition, paraoxonase, which helps to break down some OP pesticides, is an HDL-cholesterol-associated enzyme, and paraoxonase activity is related to HDL-cholesterol levels (Mackness et al., 1996), which in turn are increased with saturated and monounsaturated fat consumption and reduced with polyunsaturated and partially hydrogenated "trans" fat consump-

tion (the latter are commercially modified fats that do not occur in nature and are present in most packaged baked goods).

Cannabis (Marijuana). Two studies, one in humans and one in rats, suggest that marijuana may interact with carbamates (specifically physostigmine) to exaggerate the reaction produced—profound depression in humans and lethality in rats.

A study performed in rats showed that marijuana, or delta-9-tetrahydrocannabinol (Δ^9-THC) appeared to increase the toxicity of physostigmine (a carbamate and close analog of PB that more readily crosses the blood brain barrier) (Rosenblatt et al., 1972). Thirteen of 17 rats treated with 2 mg/kg of Δ^9-THC (in propylene glycol serum complex) and 0.4 mg/kg physostigmine salicylate died, compared with two of 17 given physostigmine salicylate (and propylene glycol serum complex) without THC ($p < 0.0002$). (Note that this was chosen to be the LD_{10} for physostigmine in Sprague Dawley rats, i.e., the dose at which 10 percent were expected to die.) It had been speculated that THC might have anticholinergic actions and thus that it might reduce the lethality of physostigmine. But instead, it augmented the lethality. Rosenblatt et al. noted that another researcher reported (in a personal communication) that THC produces a small inhibition of AChE in vivo and in vitro. Rosenblatt et al. reported that the ante-mortem and post-mortem findings were compatible with peripheral cholinergic crisis. The lethality was antagonized by atropine (two of 10 that were pretreated with 0.8 mg/kg atropine, $p = 0.006$, died) or methylscopolamine (three of 10 that were pretreated with 1 mg/kg methylscopolamine, $p = 0.02$, died).

Another study examined the impact of physostigmine in two marijuana-intoxicated patients; in both cases, physostigmine induced a profound clinical depressive reaction that was antagonized by administration of 1 mg atropine (El-Yousef et al., 1973). While physostigmine normally produces a depressive syndrome, the reaction in these two subjects "far exceeded any observed in 28 subjects of various diagnostic categories who received equal or greater amounts of physostigmine," suggesting that the THC or contaminants therein may have interacted with physostigmine, potentiating the consequent depressive state.

Cocaine. Inhibition of pseudocholinesterase (plasma cholinesterase) delays the hydrolysis of cocaine, slowing its detoxification and thus increasing the duration and magnitude of its effect. A single case report cites an episode of extreme unprovoked savage aggression, culminating in the murder of two friends, by a person who had concomitant exposures to OP and carbamate pesticides (which he sprayed as a landscaper) and cocaine (Devinsky et al., 1992). Clearly, a causal role for AChE-inhibitor exposure alone or in combination with cocaine is difficult to draw from a single case, but the existence of a mechanism of

interaction and the reported ability of each agent individually to contribute to aggressive behavior suggest that a causal interaction should be considered.

Chapter Nine

CONCLUDING REMARKS

GENERAL COMMENTS

This review of the scientific literature on specific pesticides that were identified by OSAGWI as pesticides of concern for their possible causal relationship with some of the undiagnosed illnesses seen in PGWV is intended to complement other ongoing studies, including a companion RAND project that surveyed PGWV to determine patterns of pesticide use during the Gulf War (Fricker et al., 2000). A forthcoming OSAGWI report will investigate pesticide exposures and draw conclusions based on all the available evidence.

While a review of the scientific literature can be used to develop essential hypotheses, it cannot completely substantiate or repudiate a causal link between pesticide use and illness; other factors such as actual exposure to pesticides are crucial in such a determination. To date, estimations of exposure and degree of illness have relied heavily on self-reports by PGWV. This method has several serious limitations, which have been considered and discussed in this report. The information about the potential health effects of pesticide exposure at levels reported in the literature should be useful in subsequent efforts to further characterize the role, if any, of pesticides in Gulf War illnesses.

Where possible, we have focused on reports that may be relevant to symptoms reported by some PGWV. There were no identified reports of acute exposure to pesticides that resulted in toxicity severe enough to cause PGWV to seek medical treatment during ODS/DS. The most informative literature focuses on long-term, chronic effects of reported pesticide exposures on humans. In our review, we paid particular attention to OP and carbamate pesticides, since more research and clinical findings are available concerning the role of these AChE inhibitors in long-term, chronic effects. The literature on the other classes of pesticides lacks this robustness, in some cases due to a paucity of research, but more often because long-term effects on humans have not been

consistently observed. Furthermore, previous research into PB, a carbamate used in ODS/DS for nerve-agent prophylaxis, provides some evidence of a possible role of AChE inhibitors in long-term effects similar to those experienced by some PGWV.

THE POSSIBLE CONTRIBUTION OF PESTICIDES TO HEALTH PROBLEMS REPORTED BY PGWV

The evidence in the literature is suggestive, but not conclusive, that pesticides, specifically AChE inhibitors, could be among the potential contributing agents to some of the undiagnosed illnesses seen in PGWV. Potentially supportive evidence exists in the areas of epidemiology, genetic and biological differences between ill and healthy subjects, physiological mechanisms of AChE inhibitors, and similarities between clinical findings of AChE-inhibitor-exposed subjects and reported symptoms among PGWV. Clearly, there are significant uncertainties, especially in linking these lines of evidence with actual exposures during the PGW. It is also clear that more research is needed to confirm or repudiate a causal link between pesticides (as well as other agents) and illness among PGWV. No prospective studies positively identify pesticides as causative agents of the symptoms associated with Gulf War illnesses. Recommendations for such research have been made in syntheses throughout this report, however, and are also reiterated below.

Epidemiology

Despite the uncertainties of findings in the body of epidemiological research (see Chapter Three), the literature reports putative associations between perceived pesticide exposure and increased development of chronic multisystem illness in PGWV. Several studies from the United States and the United Kingdom have shown a link between self-reported pesticide exposure and illness. Although these studies are subject to the limitation that pesticide exposure was measured by self-report, at present there has been no better meassure for pesticide exposure during the PGW. However, there is insufficient evidence to clearly define a causal link between self-reported pesticide exposure and increased likelihood of illness. If the existence of a causal link is to be adequately examined, it will be necessary to conduct studies with replications of the samples reviewed in Chapter Three. It is hoped that concurrent and subsequent studies will provide better measures for pesticide exposure during the PGW so that the reported epidemiological research can be critically revisited.

Individual Differences

Explanations for why some PGWV report illness and others do not may include differing exposures to causative agents and differing manifestations of these exposures among individuals. The issue of differing exposures is difficult to resolve due to a necessary reliance on self-reports of exposure, especially in view of the time passed since the PGW. However, the pesticide literature emphasizes the importance of individual differences in susceptibility (e.g., Leng and Lewalter, 1999). These differences can play a pivotal role in determining rates of metabolism and clinical toxicity of AChE-inhibiting agents.

Individual susceptibility to the effects of pesticides, particularly AChE inhibitors, can vary widely. The differences arise from

- Genetic differences in enzymes that contribute to metabolism and clearance of AChE inhibitors.
- Biological differences in activity of enzymes, even those enzymes whose genetic character is similar. (These differences are determined by a host of factors, some of which are environmental and many of which are unknown.)
- Other factors that influence the effect of AChE inhibitors in the body (e.g., baseline neurochemical status, itself defined by genetic and environmental factors, and membrane function, in turn determined by factors such as genetics and diet).

That these individual differences have a role in the genesis of illness is a priori likely. Some individuals exposed to certain environmental conditions became ill, while others exposed to apparently similar conditions did not. Moreover, the manifestations of illness are not completely uniform.

The finding that there are significant differences in both genetic type and activity of enzymes involved in sequestering and metabolizing AChE inhibitors between ill PGWV and healthy controls suggests a possible contribution by AChE inhibitors to reported illnesses in PGWV. The degree to which this may reflect reactions to PB rather than to carbamate and OP pesticides cannot at present be ascertained.

Future studies could seek to replicate findings of reduced activity of AChE-inhibitor detoxifying enzymes (perhaps adding chlorpyrifos oxonase and other arylesterases to the examined set) and to replicate findings of increased prevalence of low-metabolizer enzymes (K-variant, Florida variant, atypical BuChE, and paraoxonase isoforms) in ill PGWV. Studies might also focus on other factors, such as serum cholesterol and membrane fatty-acid composition, as well

as membrane fluidity, which may serve as additional cofactors in susceptibility to AChE-inhibitor effects. Further studies that evaluate whether factors like membrane fluidity or membrane composition and neurotransmitter receptor expression systematically differ between ill PGWV and controls would also be useful. The findings could serve as markers of prior susceptibility and/or as markers of chronic effects induced by OP exposure.

Interactions

There is evidence in the literature that pesticides, particularly AChE-inhibiting OPs and carbamates, may interact with—i.e., have their impact modulated by—a wide variety of conditions, including heat, foods and food constituents, recreational drugs, and pharmaceutical agents. These interactions themselves can be complicated by individual factors such as genetic differences in metabolizing enzymes, as discussed above. The differences in interacting factors are such that persons with the "same" AChE-inhibitor exposure may experience widely varying consequences. Future research could be vitally important for defining which factors and coexposures should be avoided or sought in future circumstances involving exposure to AChE-inhibiting pesticides, in both military and civilian populations. Such research is strongly recommended.

Biological Plausibility and Clinical Evidence

Evidence from the AChE-inhibitor literature suggests that administration of AChE inhibitors may lead to changes in ACh regulation beyond the obvious short-term reduction in ACh breakdown. Some of these changes resolve following cessation of exposure, at least in most of the cases studied; but other changes are long-lasting and perhaps permanent, and they may allow for indefinite changes in the regulation of ACh. Moreover, other factors (including greater age and prior exposure) may impair recovery even for those domains that might normally be fully restored.

ACh is important in the regulation of pain, sleep, muscle function, skin function, cognition, and mood—areas that figure prominently in complaints of ill PGWV. Thus, symptoms of the type seen in ill PGWV could plausibly be produced by changes in the regulation of ACh induced by exposure to AChE inhibitors. This inference offers some suggestion that AChE inhibitors, possibly including OP and carbamate pesticides, may have a role in illness in PGWV; however, it in no way precludes an important additional role of other non-AChE-inhibiting exposures.

Representative similarities in symptoms and clinical findings for ill PGWV and persons exposed to AChE-inhibiting agents are presented in the Appendix.

Compelling similarities exist in the symptom categories of fatigue, muscle and joint pain, headaches, chemical sensitivity, skin and hair effects, cognitive problems, and sleep disturbances. Apparent similarities exist both in the symptoms that are reported and in many classes of problems that are not. However, it is possible that looking at these symptoms more carefully will reveal differences between the groups; for example, the apparent similarities might turn out to be the artificial result of categorization of different "sleep" symptoms under one rubric.

The specificity of the similarities can also be questioned. It is possible that other classes of exposures might produce a similar constellation of symptoms. Exposures to organic solvents may produce symptoms most closely approximating those here, although the similarities may result in part from similar mechanisms (such as alteration in receptor expression). Although these agents do not "fit" all other identified data, such as genetic polymorphisms in enzymes that metabolize AChE inhibitors, and there is no strong reason to suppose that PGWV had greater exposure than other persons to organic solvents, an adjunctive role for organic solvents—as for other interactants—cannot be excluded. In short, there are unlikely to be many agents that would produce such similar effects in terms of both symptoms reported and symptoms and signs not present.

It would also be useful to examine the conditions that have been treated successfully by ACh-promoting drugs and the concordance between these conditions and symptoms in ill PGWV. If downregulation occurs (or if it predominates) following exposure to AChE inhibitors, then drugs that raise ACh action might lead to benefit. A sense of what the symptoms of ACh downregulation might be can be gained by examining those that have been shown to derive benefit from ACh augmentation (looking outside the PGWV setting). Insofar as there is agreement between symptoms treated by stimulating the ACh system outside the PGW setting and symptoms reported by PGWV, a connection between ACh downregulation and illness is tentatively supported. ACh agents have been used to treat fatigue and muscle weakness (Rustam et al., 1975; Trojan and Cashman, 1995a,b; Braham, 1994), memory and cognitive problems (Gray et al., 1996), diarrhea (in the special case of ulcerative colitis), Parkinson's disease, sleep apnea (Benowitz, 1996), and pain (Damaj and Martin, 1996; Donnelly-Roberts et al., 1998). Ill PGWV commonly report fatigue and muscle weakness, memory and cognitive problems, diarrhea, and sleep apnea. These data too are consistent with a possible role of ACh depression in illness in PGWV, as might be expected following AChE-inhibitor exposure.

In summary, a number of classes of symptoms have been identified in both individuals exposed to AChE inhibitors and ill PGWV. Additional data are re-

quired to further evaluate these observations, since the available research has significant limitations:

- Most studies of AChE-inhibitor exposure in humans are observational in nature, although it would probably be difficult to randomize persons exposed to OP or carbamate pesticides or persons employed in jobs entailing such exposure. Many studies are small and poorly controlled.
- Existing research on pesticide formulators and applicators is limited by the use of subjects who remain in occupations that entail exposure; this may select for the most resilient subpopulation. Those most affected may have selected themselves out of this field, through illness or intolerance.
- No identified studies entail true pre-exposure measurements: We found no prospective research that examined pesticide applicators or pesticide formulators prior to initial employment in this field and again during and after employment, compared with controls matched for age, gender, baseline intelligence and education, and other pertinent factors, tested at similar times. Such research is clearly needed.
- Few studies of OP- and carbamate-pesticide-exposed persons have systematically assessed symptoms. One study did so in a review-of-systems fashion, finding that exposed individuals scored higher in many classes of symptoms than did non-exposed comparators. This is important information and would be useful to replicate a longer time after exposure. The findings would be still more useful if more specific information within symptom categories was also elicited. A detailed cataloging of symptoms and of the comparative frequency of symptoms would be useful to enable a comparison with PGWV.

Also needed are additional studies of specific objective measures that may be changed in ill subjects with prior AChE-inhibitor exposure. Some such studies have been done, but few are well replicated or entail large samples, nor do they provide comparisons of different exposures within and outside the OP and carbamate pesticide classes.

CONCLUDING OBSERVATIONS

Evidence of the biological plausibility of AChE inhibitors as a potential cause of symptoms similar to those reported by ill PGWV suggests that these compounds could be among the potential contributing agents to some of the undiagnosed illnesses seen in PGWV. However, reliable conclusions about the possible contribution of pesticides cannot be drawn from consideration of the range of symptoms suffered by ill PGWV, although findings of relevant individual

differences among PGWV who report illness and those who do not provide additional evidence about the possible role of AChE inhibitors.

Pesticide use is so ubiquitous that studying the effect of human exposure to low-level pesticides is "difficult to investigate because of the problem of finding a pesticide-free control population" (Longo, 1980). Nevertheless, new information continues to change scientists' perception of the potential health effects of these chemicals. For example, it has been reported that the EPA will soon reduce the acceptable exposure limit for chlorpyrifos by 90 percent, based on reported brain damage in fetal rats whose mothers were exposed (*Washington Post*, June 1, 2000, p. A1). While further research can similarly provide new, stronger evidence about the role of AChE inhibitors in the genesis of illness, such lines of inquiry may not independently identify all the causes of illnesses in PGWV. This is especially true if several—or even many—causes of illness exist that are possibly interactive and manifested differently among individuals. Clearly, however, such approaches can be made more promising with increasing knowledge of actual exposure to potential causative agents, including pesticides, during ODS/DS.

Although the scientific literature has implicated exposure to AChE-inhibiting chemicals (including some pesticides) as a contributing factor in various well-defined conditions, few health problems or symptoms are uniquely characteristic of pesticide exposure. Given the evidence to date and the literature reviewed, it is inappropriate to rely upon exposure to pesticides, especially OPs and carbamates, as the explanation for the myriad health problems reported by PGWV. However, we think it equally inappropriate at this point to completely rule out pesticides as a potential contributing factor. To do so without additional research would ignore the observed similarities between undiagnosed illnesses seen in PGWV and health effects associated with pesticide exposure. It is clear that more research will be necessary to further define any causative role that pesticides may have played in the undiagnosed illnesses of PGWV.

Appendix

COMPARISON BY SYMPTOM CATEGORY OF SUBJECTS WITH AChE-INHIBITOR EXPOSURE (ORGANOPHOSPHATE OR CARBAMATE) AND ILL PGWV

Table A.1

Effects in AChE-Inhibitor-Exposed Subjects and Reported by Ill PGWV

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Autoantibodies increased	Increased autoantibodies have been reported following: • Exposures to a variety of chemicals, including pesticides (Ziem and McTamney, 1997) • Specifically OP (as well as OC) pesticides such as chlorpyrifos and malathion (Broughton, 1990; Street, 1981)	• Autoantibodies noted in some ill PGWV (Haley et al., 1997) • Increased antibodies to squalene reported (Asa et al., 2000)
Chemical sensitivity/ intolerance	• Chemical sensitivity associated with OP (and other pesticide) exposure (Miller and Mitzel, 1995; Ziem and McTamney, 1997; Rosenthal and Cameron, 1991) • OP associated with alcohol intolerance (Corrigan et al., 1994) • Associated with antibiotic sensitivity (Thrasher et al., 1993)	• MCS (multiple chemical sensitivity) increased in PGW (0.8%) vs. Bosnia deployed (0.4%) British personnel: RR 1.9 (0.8–4.4); vs. era veterans (0.3%) RR 2.2 (1.0–4.9) (Unwin et al., 1999) • 5% of Air Force PGWV vs. 2% non-deployed veterans reported chemical sensitivity: RR = 2.5, significant (Fukuda et al., 1998) • 88% of 59 consecutive evaluated veterans evaluated at Houston referral center had new chemical sensitivities (Miller and Ashford, 1999) • Canadian PGWV had increased prevalence of "symptoms of chemical sensitivity"; prevalence OR 40.01 (no CI given) (Canadian Department of National Defence, 1998)
Cognitive problems	Memory, concentration, other See list of acute and chronic effects. • Example: RR (95% CI): forgetfulness: 1.8 (1.3–2.5); loss of concentration 3.0 (2.0–4.5) (Bowler et al., 1996) • Further examples (Fukuda et al., 1998; MMWR, 1995)	Memory, concentration, other. Also see Chapter Three. • Example: British PGWV vs. era controls: crude OR (95%CI) forgetfulness 3.9 (3.5–4.5); loss of concentration 3.7 (3.2–4.2); avoiding doing things or situations 3.2 (2.7–3.7) (De Fraites et al., 1992; Unwin et al., 1999) • Example: Iowa PG Study Group: cognitive dysfunction vs. non-deployed veterans 18.7% vs. 7.6%, RR=2.5 (Iowa Persian Gulf Study Group, 1997)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Intestinal function changes	• Increased in vitro proliferation of intestinal epithelial cells (Greenman et al., 1997) • GI complaints with chlorpyrifos (Thrasher et al., 1993) • 22 Malathion-exposed vs. 21 non-exposed seamen (59%, RR 5.9, $p < 0.01$); increased abdominal pain and nausea, 50%, RR 2.0; increased change in appetite, 32%, RR 8.2 ($p < 0.01$) (Markowitz et al., 1986) • Reported symptoms in mevinphos (Phosdrin) and phosphamidon (Dimecron)-exposed workers included nausea, vomiting, abdominal pain, anorexia (Midtling et al., 1985) • Increased diarrhea, nausea, and stomach cramps after metam sodium exposure: diarrhea 50% vs. 15%, RR 3.3 (95% CI 2.0–5.7); nausea 49% vs. 9%, RR 5.4 (95% CI 2.7–10.7) (Bowler et al., 1996)	• High rate of GI symptoms: diarrhea, abdominal pain, weight loss (Roy et al., 1998) • Diarrhea in 44% of 59 symptomatic PGWV (Centers for Disease Control and Prevention, 1995) • U.S. Air Force PGWV (n = 1,163) vs. non-deployed military personnel (n = 2,538): increase chronic symptoms of gas, bloating, cramps, abdominal pain 25%, RR 3.6; diarrhea 16%, RR 5.3; weight gain ≥10 lb 15%, RR 2.5; weight loss ≥10 lb, 2%, RR 2.0; milk intolerance 7%, RR 1.75 (Fukuda et al., 1998) • 79 Reservists of 123rd Army Reserve Command abdominal pain 35%; diarrhea 32% (De Fraites et al., 1992) • 4,004 surveyed Hawaii and Pennsylvania personnel (715 active duty and 766 Reserve units who deployed; 1,576 active duty and 948 Reserve veterans who did not deploy). Reservist data: stomach upset 28%, RR 3.1; constipation 8%, RR 3.3; weight loss/gain 13%, RR 1.9 (similar RR for active duty but lower %s) (Stretch et al., 1995) • Assessment of 4 units (A–D), deployed % (prevalence ratio vs. non-deployed): diarrhea A. 27% (12.5); B. 15 %(5.3); C. 10% (3.6); D. 13% (4.1); gas, bloating, cramps, abdominal pain: A. 38% (2.7); B. 18% (1.7); C. 18% (1.9); D. 20 (2.0) (MMWR, 1995)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Irritability and aggression (see also mood and personality)	• Described with OPs and carbamates, in humans and animals (numerous small samples and case reports) (Bear et al., 1992; Dille and Smith, 1964; Gershon and Shaw, 1971; Grob and Harvey, 1953; Holmes and Gaon, 1956; Holmstedt, 1959; Metcalfe and Holmes, 1969; Namba et al., 1971; Rowntree et al., 1950)	• Air Force PGWV (vs. non-deployed) chronically moody/irritable, 36% (RR 3.6) (Fukuda et al., 1998) • U.K. PGWV vs. era: irritability/angry outbursts: OR (95%CI): 3.5 (3.2–4.0); feeling distant or cut off from others 3.2 (2.7–3.7) (Unwin et al., 1999) • 123rd Army Reserve Command (n=79): 47% report being easily irritated (De Fraites et al., 1992) • Assessment of 4 units (A–D), deployed % (prevalence ratio vs. non-deployed): A. 29% (2.9); B. 10% (5.3); C. 24% (3.4); D. 23% (3.3) (MMWR, 1995)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Pain, fibromyalgia, chronic fatigue	• Malathion-exposed vs. non-exposed seamen showed increased % (RR) of headache 73% (2.9); abdominal pain 50% (2.0); muscle or joint pain 33% (2.25) (Markowitz et al., 1986) • South African fruit-farm sprayers showed symptom % (RR vs. non-exposed) for symptoms prolonged > 3 mo: stomach pain 2% (2.0); earache 2% (2.0); pain in limbs 7% (1.75); headache 115 (2.75); and chest pain 7% (1.4) (none significant); current symptoms were significantly greater only for headache 45% (1.8) ($p < 0.05$) (London et al., 1998) • In 90 metam-sodium-exposed, %-RR (95% CI) vs. 90 non-exposed: stomach cramps/pain 40%-2.4 (1.4–4.1); chest tightness 47%-4.6 (2.4–8.7); headache > 1 day/week 64%-2.1 (1.5–3.0); joint pain or swelling 44%-2.6 (1.6–4.3) (Bowler et al., 1996)	• 3,719 CCEP registrants w/primary diagnosis of SSID, % with pain symptoms: joint pain 47%; headache 44%; muscle pain 22%; abdomen pain 16%. Similar %s were seen in 15,953 with other primary diagnoses. Chest pain: 7.1% of 9,025 with any diagnosis (Roy et al., 1998) • 1,163 U.S. Air Force PGWV vs. 2,538 non-deployed: chronic pain % (RR): headache 45% (1.4); joint pain 33% (3.0); joint stiffness 28% (3.1); abdominal pain/cramps/bloating 25% (3.6); muscle pain 18% (3.0); sore throat 15% (2.5); chest pain 5% (2.6) (all significant) (Fukuda et al., 1998) • U.K. PGWV vs. era veterans, %-OR (95% CI): headache 52%-2.1 (1.9–2.3); joint stiffness 40%-2.2 (1.9–2.4); pain in several joints without swelling/redness 32%-2.8 (2.5–3.2); chest pain 25%-2.5 (2.2–2.9); back disorders 35.7%-1.5 (1.3–1.7); migraine 18%-2.2 (1.8–2.6); arthritis 10% -1.2 (1.0–1.5) (Unwin et al., 1999) • 79 Reservists of 123rd Army Reserve Command, %: pain any joint 54%; headache 37%; abdominal pain 35%; joint pain upper extremity 33%; joint pain lower extremity 30%; pain back or neck 27% (De Fraites et al., 1992) • 3,695 phone-interviewed Iowa PGWV vs. non-deployed veterans. Fibromyalgia symptoms % (RR): 19.2% (2.0) (Iowa Persian Gulf Study Group, 1997) • 4,004 Hawaii and Pennsylvania personnel (Reserve vs. non-deployed data given; active duty data similar): % (RR): sore throat 35% (1.8); headache 47% (1.8); back problem 26% (2.0); stomach ache 28% (2.1); muscle ache/cramp 32% (2.9); aching joint/bone 35% (4.1) (Stretch et al., 1995) • 3,927 personnel from 4 units (A–D): PGWV: % (prevalence ratio vs. non-deployed): joint pain A. 38 (4.0); B. 35 (4.1); C. 29 (2.2); D. 30 (3.0); joint stiffness A. 33 (3.0); B. 26 (4.4); C. 26 (2.4); D. 26 (3.4); GI including cramps/pain A. 38 (2.7); B.18 (1.7); C. 38 (2.7); D. 18 (1.7); headache A. 43 (1.4); B. 41 (1.4); C. 42 (1.3); D. 46 (1.6) (MMWR, 1995)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Peripheral neuropathy	• 90 New York pesticide applicators: higher vibration thresholds vs. controls ($p < 0.000$; $p < 0.004$ non-dominant) (Stokes et al., 1995) • 67 Hispanic farm workers vs. 68 controls (controls may have had prior pesticide exposure): no sensory or motor NCV effects (Engel et al., 1998) • 144 farm applicators vs. 102 controls had significantly greater odds for more current peripheral nerve symptoms (OR 3.1), signs of poor coordination (OR 4.3), and absent deep tendon reflexes (OR 2.9) and reduced power (OR 2.1). Mean toe vibration threshold scores on a logarithmic scale were significantly higher among applicators (ß=0.035) and those reporting previous pesticide poisonings (ß = 0.074) (Cole et al., 1998) • 34 OP manufacturing workers in India vs. 34 controls: 58% (RR 6.6) had evidence of peripheral neuropathy, including burning sensation in the palms and feet, numbness, reduced sensitivity, poor sensory localization, muscle weakness, and sluggish tendon reflexes. Exposed had low cholinesterase levels (Ernest et al., 1995) • 8 people in a case series developed peripheral neuropathy after exterminator-applied commercial Dursban (chlorpyrifos). Among those with peripheral neuropathy alone, NCVs recovered in all cases, and sensory symptoms were improved or resolved (Kaplan et al., 1993) • 131 Dutch dithiocarbamate-exposed flower-bulb growers: Conduction velocities showed exposure-related reductions in the motor fibers of the median (–1.1 m/s) and peroneal (fast fibers: 1.2 m/s; slow fibers: –1.3 m/s) nerves, and in the sensory fibers of the median (–1.4 m/s) and sural (–0.9 m/s) nerves; one-tailed $p<0.05$, often $p < 0.01$ level. Refractory periods increased in sural and peroneal nerves (Ruijten et al., 1994) • Other reports of sensory, motor, and sensorimotor neuropathy with OP and carbamate exposure (particularly following acute toxicity) (Bidstrup et al., 1953; De Jager et al., 1981; Fisher, 1977; Hierons and Johnson, 1978; Jedrzejowska et al., 1980; Metcalf et al., 1985; Senanayake and Johnson, 1982; Senanayake and Karalliedde, 1987; Stamboulis et al., 1991; Tsatsakis et al., 1996; Umehara et al., 1991; Branch and Jacquez, 1986)	• Manchester Gulf War study: 2,221 PGWV vs. 1,964 non, % (RR) numbness and tingling: 32% (2.0) (Cherry, 1999) • 1,163 U.S. Air Force PGWV vs. 2,538 non-deployed military personnel, chronic numbness/tingling % (RR): 29% (5.8) (Fukuda et al., 1998) • 3,284 PGWV vs. 2,408 era-veterans: tingling fingers/arms: %-OR (95%CI): 25% - 2.6 (2.3–3.1) (Unwin et al., 1999)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Respiratory effects	• Chest/respiratory symptoms (CP, SOB, cough, wheeze) % (RR): 38% (2.6) (22 malathion-exposed vs. 21 non-exposed seamen) (Markowitz et al., 1986)	• Shortness of breath reported in 20% of 21,579 CCEP participants (Roy et al., 1998) • 3,284 PGWV vs. 2,408 era veterans: % - crude RR (95% CI): asthma 6.5% - 1.8 (1.3–2.3); bronchitis 4.4% - 1.8 (1.3–2.5) (Unwin et al., 1999) • 3,113 PGW deployed vs. 3,439 non-deployed Canadian forces personnel, adjusted POR (95% CI): bronchitis 2.81 (2.22–3.55); asthma 2.64 (1.97–3.55) (Canadian Department of National Defence, 1998) • 1,163 U.S. Air Force PGWV vs. 2,538 non-deployed military personnel: chronic SOB % (RR) 15% (2.5); chronic wheezing 5% (2.5) (Fukuda et al., 1998) • 79 Reservists of 123rd Army Reserve Command: cough 35% (De Fraites et al., 1992) • Iowa PGW deployed vs. non-deployed veterans (n = 3,695) % (RR): asthma 7.2% (1.8); bronchitis 3.7% (1.4) (Iowa Persian Gulf Study Group, 1997) • 4,004 Hawaii and Pennsylvania personnel: deployed % (RR vs. non-deployed) rates for Reservists: flu 23% (1.8); head cold 45% (1.7); sinus problems 46% (1.8); sore throat 35% (1.8); eye/ear/nose problem 17% (3.0); cough 23% (1.8); hoarseness 12% (3.2) (Stretch et al., 1995 • 17,248 Veterans Affairs Persian Gulf Health Registry participants: % with this as one of the top 3 complaints: SOB 7.5%; cough 3.8%; choking sensation, sneezing, mouth breathing 3.3% (Persian Gulf Veterans Coordinating Board, 1995)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Skin, hair, and dental lesions and complaints	• Rash increased in 90 metam-sodium-exposed vs. 90 non-exposed: %-RR (95%CI): 38 (11.1) (3.6–34.3) (Bowler et al., 1996) • Skin or hair problems increased in 22 malathion-exposed vs. 21 unexposed: 27%, RR 2.6. Problems with mouth, lips, or teeth: 36%, RR 2.5 (Markowitz et al., 1986) • Atopy reported in a case series of chlorpyrifos exposure (Thrasher et al., 1993) • Biological plausibility: ACh is involved in regulation of keratinocyte migration and adhesion (Grando et al., 1995; Conti-Fine and Horton, 1994) • Hair loss has been noted following carbamate exposure (non-pesticide use) (Field, 1980)	• Rash reported by 35% of 79 reservists of 123rd Army Reserve Command. Hair loss in 22%; dental complaints in 47% (including "bleeding and painful gums") (De Fraites et al., 1992) • Rash was 2nd most common complaint among 17,248 Veterans Affairs Persian Gulf Health Registry participants (cited by 17%) (Persian Gulf Veterans Coordinating Board, 1995) • Chronic rash (>6 mo) was increased in 1,163 U.S. Air Force PGWV vs. 2,538 non-deployed military personnel: rash or sores % (RR): 12% (2.4) (Fukuda et al., 1998) • Skin symptoms increased in 3,284 U.K. PGWV vs. 2,408 era veterans: %-crude OR (95%CI): dermatitis 28%-1.9 (1.7–2.2); Eczema/psoriasis 8%-1.2 (1–1.5). Hair and scalp problems higher in same group: %-crude OR (95% CI): 17% - 2.1 (1.8–2.5) (Unwin et al., 1999) • Skin irritation increased in deployed vs. non of 4,004 Hawaii and Pennsylvania personnel: data for reservists given: % (RR): 18.5% (4.7) (Stretch et al., 1995) • Rash increased in deployed vs. non from 4 assessed units (A–D) (3,927 personnel): %-PR: A. 25% 5.3; B. 15% 4.5; C. 20% 3.5; D. 19% -4.4 (MMWR, 1995) • Hair loss noted in ~13% of CCEP registrants; bleeding gums by 8% of 18,075 CCEP registrants (DoD, 1996) • Bleeding gums by 8.5% and 9.1% of 3,719 and 15,953 CCEP registrants with primary diagnoses of SSID and Other (Roy et al., 1998)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Sleep problems	• Sleep problems increased in 22 malathion-exposed vs. 21 non-exposed seamen: 50%, RR 2.0 ($p < 0.05$) (Markowitz et al., 1986) • Sleep problems increased in 164 OP-exposed South African fruit farmers vs. 83 controls: chronic for past 3 mo, % (RR): sleepiness 18% (3.6); tiredness 13 (1.9) (London et al., 1998) • Sleep problems and tiredness increased in 90 moban (carbamate) exposed vs. 90 non-exposed: %-RR (95% CI): sleep more 52%-2.6 (1.7–4.1); tired more readily 82%-1.8 (1.4–2.2); difficulty sleeping 55%-1.6 (1.1–2.2) (Bowler et al., 1996) • Sleep disturbances reported in other studies of OP- or carbamate-exposed subjects (Midtling et al., 1985; Kashyap, 1986; Richter et al., 1992) • Biological plausibility: phenyl-carbamates, which are relatively CNS-selective, have been shown in normal humans to influence REM sleep density at doses not affecting plasma cholinesterase (these have 10x greater inhibition of AChE in hippocampus and cortex than heart and skeletal muscle in rats, perhaps from preferential inhibition of G1 form of the enzyme present in higher concentrations in these brain areas; reason for greater inhibition in these areas not certain) (Weinstock et al., 1994; Holsboer-Trachsler et al., 1993)	• Sleep disorders constituted a diagnosis in 19% of 21,579 CCEP participants, and the primary diagnosis in 12%. Sleep apnea constituted a diagnosis in 5.5% and the primary diagnosis in 7.4%. 41% of the 3,719 with a primary diagnosis of SSID had symptoms of sleep disturbance; 35% of the 15,953 with another primary diagnosis had symptoms of sleep disturbance (Roy et al., 1998) • Increased current and chronic sleep problems were noted in 1,163 U.S. Air Force PGWV vs. 2,538 non-deployed personnel. For chronic symptoms, % (RR): fatigue 41% (3.2); sleep problems 25% (2.8) ($p < 0.05$ for both) (Fukuda et al., 1998) • "Unrefreshing sleep" was reported as moderate or severe in 42% of members of an Air National Guard unit in Pennsylvania (Centers for Disease Control and Prevention, 1995) • "Insomnia" was among the five most common symptoms in a health symptom checklist among 2,119 PGWV from Ft. Devens (Wolfe et al., 1998) • Increased sleep-related problems and fatigue were noted in 3,284 U.K. PGWV vs. 2408 era controls. % - crude OR (95% CI): unrefreshed sleep 56% - OR 1.8 (2.5–3.1); fatigue 51% - OR 2.7 (2.4–3.0); sleep difficulties 48% - OR 2.3 (2.1–2.6) (Unwin et al., 1999) • Fatigue and sleep disturbances were reported as among the top 3 complaints in 17% and 5% of 17,248 veterans in the Veterans Affairs Persian Gulf Health Registry (Persian Gulf Veterans Coordinating Board, 1995) • Fatigue and sleep problems increased in deployed vs. non-deployed from 4 assessed units (A–D) (39,27 personnel): %-PR: fatigue A. 54 (3.4); B. 42 (3.4); C. 36 (2.7); D. 33 (2.9); unrefreshing sleep A. 29 (2.5); B. 29 (4.6); C. 23 (2.3); D. 22 (2.5) (MMWR, 1995) • Problems falling or staying asleep were more common in 3,113 Canadian PGW than 3,439 non-deployed personnel after adjustment: 40.5%, RR 1.7 (significance not given) (Canadian Department of National Defence, 1998)

Table A.1 (continued)

Effect	Persons with Ache-Inhibitor Exposure	Ill PGWV
Temperature dysregulation	• Fever/chills were more common in 22 malathion-exposed seamen than 21 non-exposed seamen (10% vs. 0%; NS) (Markowitz et al., 1986) • Night sweats and insomnia were among the symptoms noted in 16 mevinphos (Phosdrin) and phosphamidon (Dimecron) OP-exposed cauliflower workers (no comparison group) (Midtling et al., 1985) • Perspiring for no reason was increased in 90 metam-sodium-exposed vs. 90 non-exposed persons; 33.3%, RR 4.2, 95% CI 2.0–9.1 (Bowler et al., 1996) • Fever has been reported in other studies involving OP and carbamate pesticide exposure (Gordon and Rowsey, 1998; Hirshberg ;and Lerman, 1984; Namba et al., 1971; Saadeh et al., 1996) • Biological plausibility: many studies have shown alterations, some bidirectional, in temperature regulation following OP and carbamate exposures in animal studies (Bassant, 1993; Hirshberg and Lerman, 1984; Namba et al., 1971; Saadeh et al., 1996; Gordon and Rowsey, 1998) • Delayed hyperthermia involves activation of thermoregulatory pathways that "may be similar to infection-mediated fever" (Gordon and Rowsey, 1998) • Skin temperature changes may also occur in humans exposed to carbamates or ACh augmentation and might be considered distinctly from core temperature changes (Abramson et al., 1942; Carmichael and Fraser, 1933; Ellis and Weiss, 1932; Stephenson and Kolka, 1989)	• 1,163 PGWV were more likely to have chronic soaking night sweats and chronic fever vs. 2,538 non-deployed Air Force personnel: sweats 12%, RR 6.0; fever 4%, RR 4.0 (differences significant) (Fukuda et al., 1998) • Night sweats were more common in 3,284 U.K. PGWV than 2,408 era personnel: 24.6%, crude OR 3.0 (95% CI 2.5–3.5) (Unwin et al., 1999) • Fever was reported by 13% of 79 Reservists of 123rd Army Reserve Command (De Fraites et al., 1992) • Increase in reports of chills and fever were noted in 1,481 PGW vs. 2,524 non-deployed personnel from Pennsylvania and Hawaii: Reservist PGWV 14.5% (RR 3.2) (Stretch et al., 1995)

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